Ultrasonics Sonochemistry 19 (2012) 725–728

Contents lists available at SciVerse ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultsonch

Short Communication

Glycine catalyzed convenient synthesis of 2-amino-4*H*-chromenes in aqueous medium under sonic condition

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ARTICLE INFO

Article history:
Received 24 November 2011
Received in revised form 20 December 2011
Accepted 5 January 2012
Available online 21 January 2012

Keywords:
Aldehydes
Resorcinol
Malononitrile
Glycine
Water and ultrasound

ABSTRACT

A one-pot three-component condensation of an aldehyde, malononitrile, and resorcinol has been achieved by ultrasound method. The reaction has been catalyzed by glycine in aqueous medium. This protocol afforded corresponding 2-amino-4*H*-chromenes in shorter reaction times, high yields and simple work-up procedures with the green aspects by avoiding toxic reagents.

1. Introduction

Considering the increasing environmental pollution and its drastic impact on living systems, emerging areas of green chemistry demand eco-friendly organic chemical processes [1]. Development of alternative energy sources have become a major consequence due to the consumption of energy for heating and cooling which causes a major adverse effect on the environment. In this regard, a number of organic chemists are engaged in the development of green chemistry protocols i.e. utilization of non-classical energy resources like ultrasound irradiation technique and microwave energy [2]. Use of ultrasound has proved to be one of the stepping stone towards the green syntheses. Ultrasound enhances the reactivity of the chemical reactions *via* the process of acoustic cavitation [3]. The assistance of ultrasonic irradiation efficiently shortens the reaction times. Simple experimental procedure, very high yields, increased selectivities, and clean reaction of many ultrasound-induced organic transformations offer additional convenience in the field of synthetic organic chemistry [4].

One of the major factors for a green chemical process in solution involves the choice of inexpensive, safe and non-toxic solvents. Water being abundant in nature is the first choice. In addition to satisfying the above criteria, water has also special effects on reaction arising from intra- and inter-molecular non-covalent interactions leading to assembly processes [5]. Since the pioneering studies by Breslow on Diels–Alder reactions [6], there has been profound research activity in the development of organic reactions in aqueous media which offers key advantages such as rate enhancement and insolubility of the final products, and facilitates their isolation by simple filtration. The chemical effects resulting from the irradiation of aqueous solutions with ultrasound were for the first time introduced by Loomis and co-workers [7].

Chromenes are important oxygenated heterocyclic compounds endowed with activities such as antidepressant, antihypertensive, anti-tubulin, antiviral, antioxidative activity [8,9]. Chromenes are known to activate potassium channels and inhibit phosphodiesterase IV and dihydrofolate reductases [10–17]. Chromenes are also used as cosmetics, pigments [18], and potential biodegradable agrochemicals [19]. A few procedures have been reported for the preparation of substituted 2-amino-4*H*-chromenes from resorcinol, aldehydes and malononitrile using piperazine [20], DBU [21], NEt_3 [22] and by an electrochemical synthesis in propanal [23].

In view of the inherent properties of glycine such as environmental compatibility, non-corrosives, ready availability and cost effectiveness; this catalyst has started evoking interest in the organic chemists to use it as an organo base in organic synthesis. In addition, molecules like cinchona alkaloids and other amino acids have also been used as organocatalysts in various organic syntheses, and have been proved to be highly efficient catalysts in multi-component reactions [24,25]. In continuation of our interest towards the exploration of use of glycine as an organocatalyst in organic synthesis [26a] and in the development of new synthetic methodologies [26], herein, we wish to report a one-pot multi-component synthesis of 2-amino-4*H*-chromenes from araldehydes

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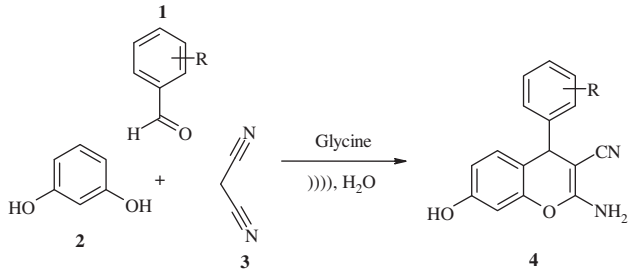
doi:10.1016/j.ultsonch.2012.01.006



Scheme 1. Synthesis of 2-amino-4*H*-chromenes under sonic condition.

(1), malononitrile (2) and resorcinol (3) at 28–30 °C in water as a solvent under sonic condition in good to excellent yield within 9–45 min (Scheme 1).

2. Methods

2.1. Materials and instruments

All starting materials were commercial products, and were used without further purification except liquid aldehydes, which were distilled before use. Yields refer to yield of the isolated products. Melting points were measured on a Raaga, Chennai, Indian make melting point apparatus. Nuclear magnetic resonance spectra were obtained on a 400 MHz Bruker AMX instrument in DMSO-d_6 using TMS as a standard. LC–Mass spectra were performed on an Agilent Technologies 1200 series instrument. HRMS analyses were carried out using ESI-Q TOF instrument. Infrared spectra were recorded using Shimadzu FT-IR-8400s spectrophotometer as KBr pellets. All the reactions were studied using SIDILU, Indian make sonic bath working at 35 kHz (constant frequency, 120 W) maintained at 28–30 °C without mechanical stirring.

2.2. General procedure for the synthesis of 2-amino-4H-chromenes

A mixture of aromatic aldehyde (5 mmol), malononitrile (5 mmol), resorcinol (5 mmol) and glycine (15 mol%) in water (5 mL) was sonicated in a sonic bath working at 35 kHz (constant frequency) maintained at 28–30 °C (by circulating water). After completion of the reaction (monitored on TLC), product was taken into ethyl acetate (10 mL) and separated. The organic layer was washed successively with water (5 mL), sat. $NaHCO_3$ (5 mL), water (5 mL) and then dried over anhydrous Na_2SO_4 to get the crude product in almost pure form. The analytical grade sample was obtained by silica gel column chromatography (EtOAc: Hexane:: 1:9).

The spectral data of some of the representative products:

2.2.1. Spectral data of **4a**

^{1}H NMR (DMSO-d_6, 400 MHz): 5.54 (s, 1H, CH); 5.95 (s, 2H, NH_2); 6.23 (s, 1H, ArH); 6.34–6.35 (d, J = 4.0 Hz, 1H, ArH); 6.74–6.75 (d, J = 4.0 Hz, 1H, ArH); 6.78–6.06 (m, 5H, ArH); 8.53 (s, 1H, OH) ppm; Mass (m/z): 264 e/z.

2.2.2. Spectral data of **4d** (Novel)

^{1}H NMR (DMSO-d_6, 400 MHz): 3.70 (s, 3H, CH_3); 4.54 (s, 1H, CH); 6.38 (s, 2H, NH_2); 6.44–6.47 (m, 2H, ArH); 6.75–6.77 (d, J = 8.0 Hz, 3H, ArH); 6.83–6.85 (t, J = 8.0 Hz, 1H, ArH); 7.05 (s, 1H, OH); 9.62 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): 34.08, 53.54, 59.53, 102.73, 105.93, 111.46, 112.65, 120.83, 129.96, 142.78, 149.53, 157.30, 157.78, 161.33 pm; HRMS (m/z): 334.0093 e/z.

2.2.3. Spectral data of **4h**

^{1}H NMR (DMSO-d_6, 400 MHz): 4.90 (s, 1H, CH); 6.51 (s, 2H, NH_2); 6.82–6.84 (d, J = 8.1 Hz, 1H, ArH); 6.99 (s, 2H, ArH); 7.60–7.66 (m, 2H, ArH); 8.01 (s, 1H, ArH); 8.07–8.09 (m, 1H, ArH); 9.75 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): 34.08, 53.54, 102.73, 105.93, 110.70, 111.46, 112.65, 120.83, 129.96, 142.78, 149.53, 157.30, 157.78, 161.33; Mass (m/z): 298 e/z.

2.2.4. Spectral data of **4j**

^{1}H NMR (DMSO-d_6, 400 MHz): 3.29 (s, 1H, CH); 4.652 (s, 2H, NH_2); 6.39 (s, 1H, ArH); 6.46–6.49 (m, 1H, ArH); 6.76–6.89 (m, 2H, ArH); 7.16–7.18 (m, 2H, ArH); 7.34–7.36 (m, 1H, ArH); 9.68 (s, 1H, OH) ppm.

2.2.5. Spectral data of **4m**

^{1}H NMR (DMSO-d_6, 400 MHz): 4.75 (s, 1H, CH); 6.13 (s, 2H, NH_2); 6.33–6.36 (d, J = 12 Hz, 1H, ArH); 6.40 (s, 1H, ArH); 6.52–6.54 (m, 1H, ArH); 6.93–6.96 (d, J = 12 Hz, 2H); 7.50 (s, 1H, ArH); 9.79 (s, 1H, OH) ppm.

2.2.6. Spectral data of **4n**

^{1}H NMR (DMSO-d_6, 400 MHz): 4.86 (s, 1H, CH); 6.38 (s, 2H, NH_2); 6.39–6.47 (m, 1H, ArH); 6.75–6.77(d, J = 8.0 Hz, 1H, ArH); 6.88 (s, 1H, ArH); 7.09–7.16 (m, 3H, ArH); 7.21–7.26 (m, 2H, ArH); 9.75 (s, 1H, OH) ppm.

3. Results and discussion

In search of the best experimental reaction condition, the reaction of 4-methoxy benzaldehyde, malononitrile, and resorcinol in the presence of glycine in aqueous medium was considered as a standard and a model reaction. When the reaction was carried out in the absence of any catalyst the product was not detected (Table 1, entry 1). In the presence of glycine the reaction was possible, and in order to determine the appropriate concentration of the catalyst used, we investigated the model reaction at different concentrations of glycine such as 5, 10, 15, and 20 mol%. The product was formed in 67%, 78%, 96%, and 94% yield, respectively (Table 1). This indicates that 15 mol% of glycine is sufficient to carry out the reaction smoothly.

In order to evaluate the effect of solvent, various solvents such as hexane, DCM, DMF, ethanol and water were used for the model reaction in the presence of glycine under sonic condition. Use of hexane and DCM yielded the Knoevenagel condensation adduct as major product and the desired product was formed only in 14% and 35%, respectively (LC–MS). Reaction in DMF and ethanol resulted in 86% and 82% yields, respectively. As I_{max} (maximum cavitation intensity) and T_{Imax} (the temperature at which I_{max} is reached) of any solvent has a profound effect in sonochemical reactivity (for water I_{max} is 100), I_{max} of water is responsible for the increase in the reaction rate compared to the other solvents for which I_{max} is less [27]. Further, when the transition state or the product is more polar than the reactants then polar solvents stabi-

Table 1
Evaluation of catalytic activity of glycine in the synthesis of 2-amino-4*H*-chromene.[a]

Entry	Amount of glycine (mol%)	Time (min)	Yield (%)[b]
1	0	36	ND
2	5	18	67
3	10	18	78
4	15	9	96
5	20	9	94

[a] Reaction condition: resorcinol (2 mmol), 4-methoxybenzaldehyde (2 mmol), malononitrile (2 mmol) and glycine under sonication.
[b] Isolated yields.

Table 2
Effect of solvent on the rate of the reaction and yield of the product.[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	Solvent-free	54	5
2	Hexane	36	14
3	DCM	36	35
4	DMF	18	86
5	Ethanol	18	82
6	Water	18	95

[a] Reaction condition: aromatic aldehyde (2 mmol), malononitrile (2 mmol), resorcinol (2 mmol) and glycine (15 mol%) and water (5 mL).
[b] Isolated yield.

Table 3
Synthesis of 2-amino-4*H*-chromenes from aromatic aldehydes, resorcinol, malononitrile and catalytic glycine under aqueous sonic condition.

Entry	Aldehyde	Product[a]	Time (min)	Yield[b] (%)
1	H	**4a**	9	94
2	4-OMe	**4b**	18	91
3	3,4-$(OMe)_2$	**4c**	27	92
4	3-OMe,4-OH	**4d**	30	92[c]
5	4-Me	**4e**	24	90
6	4-OH	**4f**	20	95
7	3,4-O–CH_2–O–	**4g**	36	88
8	4-Cl	**4h**	16	92
9	2-Cl	**4i**	27	92
10	4-F	**4j**	20	91
11	2-F	**4k**	18	92
12	3-NO_2	**4l**	36	89
13	2-NO_2	**4m**	32	90
14	2-Furfuryl	**4n**	36	96
15	2-Thiophene	**4o**	45	93

[a] Reaction condition: resorcinol (2 mmol), aromatic aldehyde (2 mmol), malononitrile (2 mmol) and glycine (15 mol%) under sonication.
[b] Isolated yields.
[c] Novel compound.

Table 4
Reproducibility of the optimized reaction.[a]

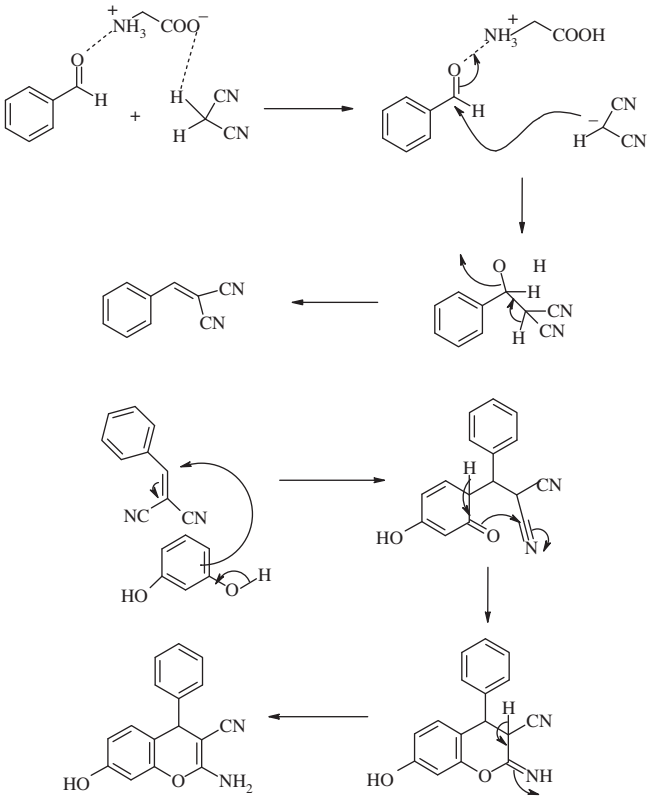
Entry	Aldehyde	Product	Time (min)	Yield[b] (%)
1	H	**4a**	9	94
2	H	**4a**	18	93
3	H	**4a**	27	94
4	4-OH	**4f**	30	95
5	4-OH	**4f**	24	95
6	4-OH	**4f**	24	93

[a] Reaction conditions: resorcinol (2 mmol), aromatic aldehyde (2 mmol), malononitrile (2 mmol) and glycine (15 mol%) under sonication.
[b] Isolated yields.

lize the transition state. The more polar the solvent the faster the reaction will be. Hence, compared to non-polar solvents polar solvents like DMF and ethanol enhanced the rate of the reaction and gave products in good yields.

The reaction was also studied under solvent-free condition and only trace amount of the desired product was obtained, which clearly indicates that, water is essential for shifting the reaction to the product side. In the presence of water, the reaction not only went to completion efficiently but also furnished the product in excellent yield (95%, Table 2).

For assessing the generality of optimized reaction condition, a wide range of substituted aldehydes were allowed to undergo this three-component condensation. Aromatic aldehydes with electron-withdrawing and electron-donating functionalities such as Cl, F, OH, Me, OMe, and NO_2 (Table 3, entries 2–13) were found to be compatible under the optimized reaction condition. Heteroaromatic aldehydes such as thiophene-2-carbaldehyde and



Scheme 2. A plausible mechanism of formation of 2-amino-4*H*-chromenes.

furan-2-carbaldehyde were equally amenable to these conditions (Table 3, entries 14 and 15). All the results are summarized in Table 3. Formation of the product was confirmed with the help of IR, ^1H NMR, and mass spectral analysis or comparison of the melting points with the products prepared by reported methods [20,21].

The reproducibility of the reaction has also been checked for three times each for benzaldehyde and 4-hydroxybenzaldehyde. It was found that, every time the optimised reaction condition holds good for the synthesis of aminochromenes. These results have been presented in Table 4.

The reaction is expected to proceed *via* the Knoevenagel condensation of an aromatic aldehyde and malononitrile, followed by the cyclo-condensation reaction with resorcinol in water to form the desired product as shown in Scheme 2.

Further experiments were designed for investigating the influence of ultrasound on the synthesis of 2-amino-4*H*-chromenes (Table 5). Representative reactions were carried out with benzaldehyde and aromatic aldehydes containing functional groups like NO_2, OH, OMe; separately in water (5 mL) using glycine (15 mol%) as the catalyst at 28–30 °C with magnetic stirring in the presence and absence of ultrasound and found that 25% chromene was obtained for the condensation of benzaldehyde, resorcinol and malononitrile in the absence of ultrasonic irradiation; the Knoevenagel condensation product-arylmethylidenemalononitrile and the unreacted resorcinol were isolated. Whereas 94% yield of aminochromene was obtained under the influence of ultrasound, indicating that this one-pot condensation reaction can be greatly accelerated under sonic condition.

Upon irradiation with ultrasound, the formation, growth, and implosive collapse of bubbles can create extreme physical and chemical conditions in liquids [27a], leading to short-lived localized hot-spots which produce relatively high temperature for this condensation reaction to occur, and the rate of the reaction got well accelerated under sonic condition. In the present reaction,

Table 5
Synthesis of 2-amino-4*H*-chromene derivatives catalyzed by glycine[a] under silent and sonic conditions.

Entry	R_1	Product (**4**)	Time/yield (◠, min/(%))[b]	Time/yield (min/(%))[c]
1	H	**4a**	9/25	9/94
2	4-OMe	**4b**	20/40	18/91
3	4-OH	**4f**	30/47	20/95
4	3-NO_2	**4l**	20/35	36/89
5	2-NO_2	**4m**	40/45	32/90

[a] Reaction condition: aromatic aldehyde (2 mmol), malononitrile (2 mmol), resorcinol (2 mmol), glycine (15 mol%) and water (5 mL).
[b] Silent.
[c] Sonication.

got well accelerated under sonic condition. In the present reaction, the reactants are partially dissolved initially, and the reaction begins only under the influence of ultrasound which can be explained as follows: when cavitation occurs near the solid surface (of solid substrates), cavity collapse is non-spherical and as a result of this a liquid jet will be formed which is targeted at the surface. Depending upon the conditions used, this powerful jet can also activate the catalyst by heat transfer to the surface through disruption of interfacial boundary layers. At a liquid–liquid interface (heterogeneous), the intense movement due to the liquid–jet formation also leads to the mutual injection of droplets of one liquid into the other one, producing emulsions as in the present reaction. These emulsion droplets are smaller in size and hence the overall reactant contact surface gets increased. The driving force for the increased efficiency of formation of 2-amino-4*H*-chromenes under sonic condition is because of the increase in the temperature due to the formation of hot spots; and due to increase in the reactant contact surface area through cavitation phenomenon [4,27].

4. Conclusions

An ultrasound-assisted method for the synthesis of 2-amino-4*H*-chromene derivatives is studied in details. This one-pot condensation reaction, leading to a series of polysubstituted chromenes can be carried out efficiently using glycine as an organocatalyst in water as solvent. Ultrasound accelerates greatly the reaction rate and enhances the yields. The method described in this paper is mild and energy efficient and provides a very reliable procedure for the synthesis of 2-amino-4*H*-chromene derivatives.

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