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An efficient synthesis and antimicrobial and antifungal activities of disubstituted 3,4-dihydro-2*H*-1,3-thiazin-4-ones using lemon juice: A natural approach

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Abstract

An efficient and greener approach has been developed for the synthesis of 6-arylamino-5-cyano-2,3-dihydro-1,3-thiazin-4(1*H*)-ones, using Lemon juice as a natural catalyst. It was prepared *via* condensation of 3-arylamino-2-cyano-3-mercaptoacrylamides with several of aldehydes. The reaction proceeded in short period of time with excellent yields. Most of the synthesized compounds were tested in vitro against four bacterial strains, Bacillus thuringiensis, Micrococcus roseus, Escherischia coli and Pseudomonas aeruginosa and two strains of fungi, Aspergillus niger and Penicillium italicum. Biological evaluation of the prepared products showed that many of them revealed promising antimicrobial activity.

1. Introduction

In recent years, environmentally benign synthetic methods have received considerable attention and some green protocols have been developed. Many synthetic chemists have made a great deal of effort to design sustainable and clean procedures to replace the classical synthetic methods [1]. The growing concern for the environment demands, the development of eco-friendly and economic processes wherein even less hazardous byproducts are not desirable. Numbers of organic reactions are reported in the literature by employing natural catalyst like clay, [2-4] phosphates [5-7] etc. Today, there is a great demand for green and inexpensive acids instead of conventional mineral acids such as HF, HCl, and H_2SO_4 in chemical processes. Mineral acids are corrosive and hazardous catalysts [8]. Fruit juice of Citrus lemon as a natural catalyst, due to its acidic nature (pH about 2-3) has been found to be a suitable replacement for various homogenous catalysts. Easy preparation and handling, separation and work-up processes, non-hazardous nature and easier waste material are among the most common characteristics that make it green catalyst. 1,3-Thiazines are an important type of heterocyclic showing a wide variety of pharmacological properties. Thus, 1,3-thiazine derivatives have recently been reported as cholecystokinin antagonists [9], anti-mycobacterial agents [10], cannabinoid receptor agonists [11], and inhibitors of NO synthase (NOS) as antibacterial [12], antipyretic [13], anti-inflammatory [14,15], analgesic [16], antitumor [17], antioxidant agents [18] and as calcium channel modulators [19]. Furthermore, the antibiotic activity of cephalosporin is due to the presence of the 1,3-thiazine moiety[20]. In continuation of this research, I herein report the first example of the synthesis of 2,3-dihydro-1,3-thiazin-4-one derivatives and evaluated their biological activities in presence of fruit juice of Citrus lemon a green, inexpensive and easily available acid catalyst by condensation 3-arylamino-2-cyano-3-mercaptoacrylamides with various of aromatic aldehydes.

2. Experimental details

All the chemicals used in the present study are of analytical grade and were obtained from local suppliers.

2.1 Preparation of fruit juice from the fruits of Citrus lemon

Fruits of Citrus lemon were purchased from the local market. The fruit's juice was extracted mechanically and centrifuged using Micro Centrifuge (REMI RM-12C). The clear portion of the juice was used as catalyst for the reactions (with a concentration 100%).

*2.2 General procedure for the synthesis 6-arylamino-5- cyano-2,3-dihydro-1, 3-thiazin-4(1H)-ones **3a-m**:*

2.2.1 Method (A)

To a mixture of 3-arylamino-2-cyno-3-mercaptoacrylamides **1** (1 mmol) and aromatic aldehydes **2** (1 mmol) taken in round bottam flask was added 5 mL Lemon juice and the reaction mixture was stirred at room temprature for the time indicated in Table1. The progress of the reaction was checked by TLC (ethyl acetate:n-hexane, 1:9). After completion of reaction, the solid residue was washed with ethanol. The obtained solid was collected by filtration and purified by recrystallization from DMF/EtOH (1/3).

Table 1. Lemon juice catalyzed synthesis of 2,3-dihdro1,3-thiain-4(*H*)-ones **3a-m**.

Entry	R_1	R_2	Product (**3**)	Yield (%) (a/b)	Time (min) (a/b)	M.P. (ºC)	Ref
1	C_6H_5-	C_6H_5-	**3a**	78/89	60/30	265	22
2	C_6H_5-	4-CH_3-C_6H_4-	**3b**	82/90	55/25	252	22
3	C_6H_5-	4-CH_3-O-C_6H_4	**3c**	88/93	50/20	245	22
4	C_6H_5-	3- NO_2-C_6H_4	**3d**	88/94	45/35	239	22
5	C_6H_5-	4-Cl-C_6H_4-	**3e**	81/90	51/30	254	22
6	C_6H_5-	2,4-dichloro-C_6H_4-	**3f**	88	55/20	347	22
7	C_6H_5-	1-naphthyl-	**3g**	89/95	44/35	251	---
8	C_6H_5-	4-Br-C_6H_4-	**3h**	86/92	55/30	260	22
9	C_6H_5-	3,4-dimethoxy-C_6H_4-	**3i**	88/94	50/25	212	22
10	C_6H_5-	Thiophen-2-yl	**3j**	87/94	70/40	230	22
11	C_6H_5-	Cyclohexyl	**3k**	87/93	45/35	236	22
12	C_6H_5-CH_2-	4- CH_3-O-C_6H_4	**3l**	88/92	40/30	211	21
13	C_6H_5-CH_2-	1-naphthyl-	**3m**	87/96	55/30	246	--

2.2.2 Method (B)

To a solution of 3-arylamino-2-cyno-3-mercaptoacrylamides **1** (1 mmol) and aromatic aldehydes **2** (1 mmol) in 5 mL EtOH: H_2O (1:1), 2 mL Lemon juice was added and the reaction mixture was reflux for the time indicated in Table1. The progress of the reaction was checked by TLC (ethyl acetate:n-hexane, 1:9). After completion of reaction, solvent was removed.

2-(Naphthalen-1-yl)-4-oxo-6-(phenylamino)-3,4-dihydro-2H-1,3-thiazine-5-carbonitrile (3g)

Yield 95% (method B); mp 251◦C; IR (ν/cm^{-1}): 3320, 3180 (NH), 2220 (CN), 1670 (C O);^{1}H NMR (500 MHz, DMSO-d^6) δ: 10.23 (s, 1H, N*H*), 8.54 (d, *J*=2.8 Hz, 1H, N*H*), 7.46 (d, *J*=8.0 Hz, 2H, H_{Ar}), 7.40 (t, *J*=7.2 Hz, 3H, H_{Ar}), 7.36 (d, *J*=8.0 Hz, 2H, H_{Ar}), 7.26 (t, *J*=7.6 Hz, 3H, H_{Ar}), 7.20 (d, *J*=7.6 Hz, 2H, H_{Ar}), 6.92 (d, *J*=2.9 Hz, 1H, C*H*); ^{13}C NMR (500 MHz, DMSO-d^6), 174.20 (C_{Ar}), 166.48 (*C*O), 138.26 (C_{Ar}), 134.93 (C_{Ar})133.93 (C_{Ar}) , 133.52 (C_{Ar})131.15 (C_{Ar}), 130.50 (C_{Ar}) , 130.11 (C_{Ar}), 129.39 (C_{Ar}), 129.34 (C_{Ar}), 127.29

(CAr), 127.18 (CAr), 126.81(CAr), 126.70 (CAr), 125.84 (CAr), 125.74 (CAr), 124.04 (CAr), 116.92 (CN), 77.81 (CAr), 56.65 (CH) ; Calcd for C21H15N3OS: C 70.57, H 4.23; N 11.76;O; 4,48 ; S; 8.97 found: C 70.59, H 4.25; N 11.74; O; 4,50 ; S; 8.96.

6-(Benzylamino)-2-(naphthalen-1-yl)-4-oxo-3,4-dihydro-2H-1,3-thiazine-5-carbonitrile (3m)

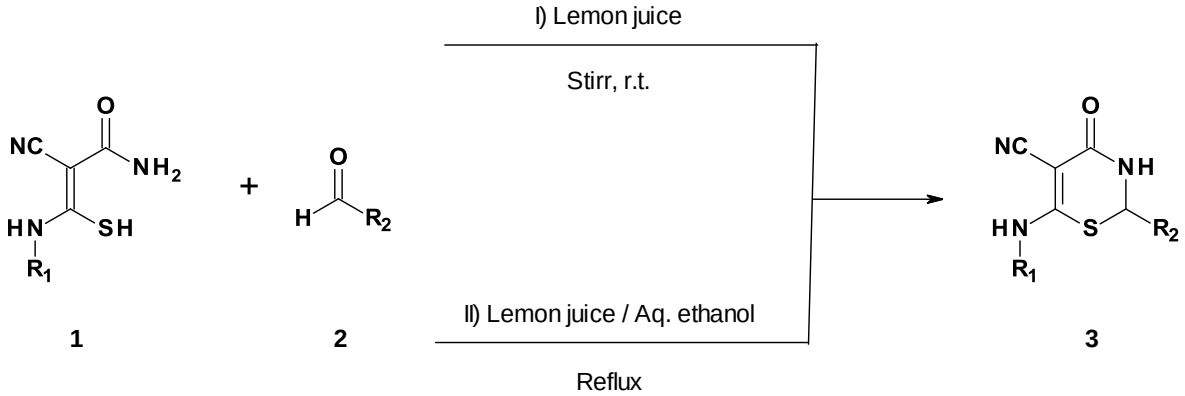
Yield 96% (method B); mp 246◦C; IR (ν/cm^{-1}): 3340(NH), 2230 (CN), 1660 (C O); ^{1}H NMR (500 MHz, DMSO-d^{6}) δ: 8.97 (t, *J*=6.2 Hz 1H, N*H*), 8.46 (d, *J*=7.99 Hz, 2H, H_{Ar}), 8.31 (d, *J*=2.1 Hz, 1H, N*H*), 8.00-7.98 (m, , 3H, H_{Ar}), 7.72 (d, *J*=8.10 Hz, 2H, H_{Ar}), 7.60-7.52 (m, 3H, H_{Ar}), 7.34-7.17 (m, 2H, H_{Ar}), 6.89 (d, *J*=2.8 Hz, 1H, C*H*), 4.46 (dd, *J*=16.0 Hz, 2H, CH_2) ; ^{13}C NMR (500 MHz, DMSO-d^{6}), 173.35 (C^{6}), 166.48 (*C*O), 138.26 (C_{Ar}), 134.04 (C_{Ar}) , 133.93 (C_{Ar}) , 132.06 (C_{Ar}) 131.15 (C_{Ar}), 130.50 (C_{Ar}) , 130.11 (C_{Ar}), 129.39 (C_{Ar}), 129.34 (C_{Ar}), 127.29 (C_{Ar}), 127.18 (C_{Ar}), 126.81(C_{Ar}), 126.70 (C_{Ar}), 125.84 (C_{Ar}), 125.74 (C_{Ar}), 124.04 (C_{Ar}), 116.92 (*C*N),77.81 (C_{Ar}), 56.65 (*C*H) ; 48.50 (*C*H_2) ; $C_{22}H_{17}N_3OS$: C 71.41, H 4.61; N 11.31; O; 4,31 ; S; 8.63 found: C 71.44, H 4.62; N 11.32; O; 4,32 ; S; 8.65

2.2.3.Measurements

Melting points were determined on a Kofler block and uncorrected. IR spectra were recorded on Perkin Elmer FT-IR Spectrophotometer (Spectrum RX 1) and Jasco FT-IR-4200 Spectrophotometer as KBr pellets. ^{1}H NMR spectra were obtained in CDCl3 or DMSO-d6 on a Bruker AV-300 (300 MHz) and Bruker AV500 (500 MHz) spectrometers using TMS as an internal standard. Mass spectra were acquired on a QTOF Micro Mass spectrometer. Analytical samples were dried in vacuo at room temperature. Microanalytical data were recorded on two Perkin-Elmer 2400 Series II C, H, N analyzers. Column chromatography were performed on silica gel (100-200 mesh) using petroleum ether (60-80ºC)-ethyl acetate mixture as eluents. TLC was carried out on silica gel G.

3. Results and Discussion

We have demonstrated the condensation of 3-arylamino-2-cyno-3-mercaptoacrylamides **1** with various types of aldehydes **2** affording 6-arylamino-5- cyano-2,3-dihydro-1,3-thiazin-4(1*H*)-ones **3** by using lemon juice as natural acid catalyst (Table 1). Here Lemon juice extract is not only worked as catalyst, but also as solvent medium. (Method A) In our investigation, we observed the smooth applicability of protocol with various substituted aromatic aldehydes. Many of the reported synthetic methods are associated with the use of expensive reagents, multistep reaction, longer reaction time, high reaction temperature and tedious work-up procedures. Thus, development of a facile, atom-efficient, greener, eco-friendly method is highly desirable.



Scheme 1. Reaction Conditions: I) Method (A) Lemon juice, (Const. Stirr, r.t.)
II) Method (B) Lemon juice, Aq. Ethanol (50%), reflux.

As literature tells us that the 2,3-dihydro-1,3-thiazin-4(1*H*)-one derivatives were best synthesized in the presence of acid catalysts, we have investigated here an efficient and environmentally benign protocol for the synthesis of 2,3-dihydro-1, 3-thiazin-4(1*H*)-ones using lemon juice as natural acid catalyst. Lemon is very cheap and easily available material. Main contents of the lemon extract are moisture (85%), carbohydrates (11.2%),

citric acid (5-7%), protein (1%), vitamin-C (0.5%), fat (0.9%), minerals (0.3%), fibers (1.6%) and some other organic acids. As lemon juice is acidic in nature (pH about 2-3), having 5-7% citric acid as the predominant acid value and, it would have been worked as acid catalyst for condensation. In summary, it can be stated that the present green synthetic protocol is highly efficient as it avoids the use of hazardous solvents at any stage of the reaction. As cited in Scheme 1, not only does the use of water as solvent allow for rapid reactions, but also the products are often insoluble in water, facilitating their ready isolation.

Most of these products are well-characterized except **3g** and **3m** which were almost fully elucidated in this study using IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. The remain products are known; their physical and spectroscopic data (IR and ^{1}H NMR) were compared with those reported in the literature [21,22] and found to be identical.

3.1 Antimicrobial and antifungal activities

Most of the prepared compounds were tested in vitro against four bacterial strains, Bacillus thuringiensis, Micrococcus roseus, Escherischia coli and Pseudomonas aeruginosa and two strains of fungi, Aspergillus niger and Penicillium italicum. The technique was performed using the filter paper disc method [23-26]. Examine petri dishes were incubated at 30ºC for 24 hours in case of bacteria and 72 hours for the tested fungi and 3% concentration of each sample, dissolved, in DMF *(N,N*-Dimethylformamide). Results are presented in the Table 2.

Table 2. Antimicrobial and antifungal activities of synthesized compounds.

Comp. (100µg/ml	Antimicrobial				Antifungal	
	Gram-positive bacteria		Gram-negative bacteria			
	Bacillus thuringiensis	*Micrococcus roseus*	*Escherischia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Penicillium italicum*
3a	N	+	N	N	N	N
3b	N	+	+	N	N	N
3c	+	++	+++	+++	+++	+++
3d	N	N	N	N	N	N
3e	+	++	+++	+++	+++	+++
3f	++	+	+	+	N	N
3g	N	++	++	+	+	+
3h	++	++	+++	+++	+++	+++
3i	+	+	+	+	N	N
3j	+++	++	+++	+	++	+
3k	++	++	+	+	++	+++
3l	++	++	+	+	+++	++
3m	N	N	N	N	+++	+++

- N = No effect.
- Diameter of no growth zone:
- + = till 0.5 Cm;
- ++ = till 1.0 Cm;
- +++ till 2.0 Cm.
- Sample concentration = 3% , dissolved in *N,N*-dimethylformamide.

Conclusion

In the present investigation, we have developed an efficient and environmentally benign synthesis of arylamino-5-cyano-2,3-dihydro-1,3-thiazin-4(1*H*)-ones at room temperature by applying Lemon juice as a natural acid catalyst. The efficiency of the methodology towards various substituted aldehydes is very good viz. fast reaction rate and the excellent yield. Some of the synthesized compounds were evaluated for their antibacterial and antifungal activities in vitro against four bacteria and two fungi.

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