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Microwave-assisted green synthesis of 1,3-thiazines as potential antifungal agents using lemon juice

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Abstract

A new derivatives 6-arylamino-5-cyano-2,3-dihydro-1,3-thiazin-4(1H)-ones is designed as potential antifungal agents. Synthesis of 6-arylamino-5-cyano-2,3-dihydro-1,3-thiazin-4(1H)-ones s was carried out by the condensation of 3-arylamino-2-cyano-3-mercapto-acrylamides with various aldehydes under microwave irradiation using and lemon juice as a natural catalyst and solvent. Synthesized compounds were characterized on the basis of IR, ^{1}HNMR, ^{13}CNMR, mass and analytical data. Some of synthesized compounds were screened in vitro for antifungal activity by inhibitory action against four fungal strains like *Fusarium oxysporum, Aspergillus niger, Verticillium dahliae and Aspergillus flavus* . Most of the synthesized compounds have shown good antifungal activities.

1. Introduction

Thiazines are an important type of heterocyclic compounds owing to their biological activities that showed a wide variety of pharmacological properties. 1,3-thiazine derivatives have recently been reported as cholecystokinin antagonists [1], antimycobacterial agents [2], cannabinoid receptor agonists [3], inhibitors of NO synthase (NOS) as antibacterial [4], antipyretic [5], anti-inflammatory [6,7], analgesic [8], antitumor [9], antioxidant agents [10] and calcium channel modulators [11]. Furthermore, the antibiotic activity of cephalosporin was ascribed to the presence of 1,3-thiazine moiety[12]. In addition, the microwave is one of the most important methods used in green chemistry. Microwave are used to turn chemical reactions within the laboratories that led scientists to explore the mechanism of microwave electrical phenomenon and to acknowledge the advantages of the technique for chemical synthesis [13-14]. During the past decade, microwaves have been widely used for carrying out chemical reactions and have become a valuable non-conventional energy source for operating organic synthesis [15-16]. It is worth noting that microwave chemistry was frequently used only when all other options to realize a specific reaction had failed, or when excessively long reaction times or high temperatures were required to complete a reaction. Due to the increasing availability of microwave reactors in many laboratories, routine structural transformations are being carried out by heating the microwave [17-18]. Lemon juice is widely used in various fields. Including medical use to control high blood pressure and asthma, and to prevent kidney stones. It is also a known plant species for antioxidant activity as well as for anti-cancer activity. Citric acid and ascorbic acid (vitamin C) are also considered to be responsible for acting as a natural acid catalyst in organic synthesis. It is also known that the use of microwave radiation has many of the following advantages compared to conventional heating: including but not limited to such as increasing the speed of chemical reactions as uniform heating occurs throughout the material, the process speed is increased, and there is higher efficiency in reducing heat generated by side reactions Unwanted, is better, can improve reproduction, there is a reduction in waste resulting from heating reaction how much can avoid environmental heat loss [19]. In view of the above mentioned findings, and following our recent work to

develop neat methodologies in synthetic chemistry, we report an efficient and environmentally benign protocol for the condensation reaction of 3-arylamino-2-cyano-3-mercaptoacrylamides 1 with various of aldehydes 2 to synthesize 2,3-dihydro-1,3-thiazin-4-one derivatives 3a-t using lemon juice as natural acid catalyst under microwave irradiation. The effect of some 1,3- thiazine derivatives 3a-t on certain pathogenic fungi of plants was studied. The focus was on some fungus that affects olive trees and palms in Al-Jouf region, especially *Verticillium dahliae and Fusarium oxysporum*. Moreover the effects of 1,3-thiazine derivatives on some fungus such as *Aspergillus niger and Aspergillus falves* were also studied. These compounds were screened for their anti-fungal activity and results were reported [20-22]

2. Material and Methods

All chemical were from Merck Co. and used as obtained such. Thin Layer Chromatography data were collected at 254 nm for samples using Analytical Merck (9385) sheets of aluminum-silica using a PF254 as an indicator. A Stuart-electro thermal cell was used to determine m.p. of samples and infrared spectra experiments were run using potassium bromide pellets on a Bruker IR machine, Faculty of Science, Jouf University. NMR spectra were measured on a Bruker AV-400 spectrometer (400 MHz for 1H, 500 MHz for 13C) at Sattam Bin Abdulaziz University Saudi Arabia. Electron impact mass spectra were recorded with a JEOL JMS-600 spectrometer at an ionization voltage of 70 eV at the Central Lab, at National Research Center, Dokki, Cairo, Egypt. The elemental analyses were carried out in Micro analytical Center, Assuit, Egypt.

Starting materials

3-arylamino-2-cyno-3-mercaptoacrylamides (1)

It was prepared according to published procedures [23].

2.*1 Fruit juice*

Fruit juice was prepared from citrus lemon fruits of Citrus lemon was purchased from the local market. The fruit's juice was extracted mechanically and centrifuged using Micro Centrifuge (REMI RM-12C). The juice which used as catalyst in the reaction appeared as clear portion

2.2 General methods for the preparation 6-Arylamino-5- cyano-2, 3-dihydro-1, 3-thiazin-4(1H)-ones 3a-t.

A mixture of 3-arylamino-2-cyno-3-mercaptoacrylamides 1 and aromatic aldehydes 2 and lemon juice (2 ml) was mixed properly with the help of glass rod and irradiated in a microwave oven at (120 °C, 360W), as time indicated in Table 1. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 7:3). After completion of the reaction, the reaction mixture was cooled and ice/water (30 ml) was added. . The obtained solid was collected by filtration and purified by recrystallization from DMF/Ethanol (1/4) to afford the pure corresponding 2,3-dihydro-1, 3-thiazin-4(1H)-one derivatives 3(a-t). All the products were characterized by their spectral data. The compounds 3a -3l and are known; their physical and spectroscopic data (IR and 1H NMR) were compared with those reported in the literature [23-25] and found to be identical, where remain products are well-characterized fully elucidated in this study using IR, 1H-NMR, ^{13}C-NMR, and elemental analysis.

6-(Benzylamino)-3,4-Dihydro-4-oxo-2-phenyl-2H-1,3-thiazine-5-carbonitrile (3m)

Pale yellow crystals, m.p. 128—130 ℃; IR (ν/cm^{-1}): 3350- 3260 (NH), 2231 (CN), 1658 (C O): ^{1}H nmr (DMSO-d_6): δ H = 4.45 (dd, J＝16.0 Hz, *2H*, CH_2), 6.21 d (1H, CH, *J*=2.5 Hz), 7.18–7.38 m (10H, Ar- H), 8.45 d (1H, NH, J=2.5 Hz), 9.15 (t, 1H, NH); ^{13}C nmr (DMSO-*d6*): $_{\delta}$C = 48.04 (CH_2), 58.18 (CH), 74.43 (C5), 117.50 (CN), 125.99, 127.47, 127.67, 128.37, 128.66, 128.85, 129.11, 129.37, 129.58, 135.11, 137.08, 138.24 (C-Ar$_{)}$, 166.04 (C O), 167.56 (C6) ppm. Anal. Calcd. For $C_{18}H_{15}N_3OS$: C, 67.27; H 4,70; N, 13,07; O, 4,98; S, 9,98. Found: C, 67.28; H 4,69; N, 13,11; O, 5,01; S, 10,00 ;

6-(Benzylamino)-3,4-Dihydro-4-oxo-2-p-tolyl-2H-1,3-thiazine-5-carbonitrile (3n)

Pale yellow crystals, m.p. 253- 254°C; IR (ν/cm^{-1}): 3340(NH), 2215 (CN), 1655 (CO);. ^{1}H nmr (DMSO-*d6*): δ H = 8.98 (t, *J*＝6.2 Hz *1H*, NH),), 8.49 (s, 1H, NH), 7.38 (d, J＝8.0 Hz, 2H, Ar- H), 7.34 (d, J＝8.0 Hz, 2H, Ar-H), 7.25 (d, J＝8.0 Hz, 1H, Ar-H), 7.20 (d, J＝8.0 Hz, 4H, Ar-H), 6.08 (d, J＝2.8 Hz, 1H, CH), 4.48 (dd, J＝16.0 Hz, 2H, CH_2), 2.29 (s, 3H, CH3); ^{13}C nmr (DMSO-*d6*): *δ* C = 21.18 (CH_3), δ 48.50 (CH_2), 58.47 (CH), 74.40 (C5),117.52 (CN), 125.97, 127.48, 127.63, 127.88,128.03,128.64, 129.62, 130.08, 130.21, 133.93,138.28, 139.16, (C-Ar), 166.05 (C O), 171.21 (C6) ppm. Anal. Calcd. For $C_{19}H_{17}N_3OS$: C, 68.03; H, 5.11; N, 12.53; O, 4.77; S, 9.56. Found: C, 68.04; H, 5.12; N, 12.55; O, 4,80; S, 9. 56.

6-(Benzylamino)-3,4-Dihydro-2-(4-methoxyphenyl)-4-oxo-2H-1,3-thiazine-5-carbonitrile (3o)

This compound is known and its physical and spectroscopic data were compared with those reported in the literature [23]

6-(Benzylamino)-2(-3,4-Dichlorophenyl)-3,4-Dihydro-4-oxo-2H-1,3-thiazine-5-arbonitrile (3p)
Pale yellow crystals, m.p. 212-214 ℃; IR (ν/cm^{-1}): 3350, 3260 (NH), 2230 (CN), 1660 (C O); ^{1}H nmr (DMSO-*d6*): δ H = 9.05 (t, J＝6.2 Hz *1H*, NH), 8.46 (d, J＝7.99 Hz, 2H, Ar- H), 8.54 (d, *J*＝2.8 Hz, *1H*, NH), 7.18–7.55 m (10H, Ar- H), 6.13 (d, J＝2.8 Hz, 1H, CH); 4.44 (dd, J＝16.0 Hz, 2H, CH_2): ^{13}C nmr (DMSO-*d6*) δC = 48.50 (CH_2), 56.44 (CH), 77.40(C5), 117.41 (CN), 125.62, 127.39, 127.56, 127.91, 128.63, 129.01, 129.39, 131.16, 131.65, 131.96, 138.12, 139.27, (C-Ar), 165.53 (CO), 166.71(C6) ppm. Anal. Calcd. for $C_{18}H_{13}Cl_2N_3OS$: C, 55,39; H, 3,36; N, 10,77; O, 4,10; Cl, 18,17; S, 8,22; Found: C, 55,39; H, 3,37; N, 10,78; O, 4,11; Cl, 18,19; S, 8,23.
6-(Benzylamino)-3,4-Dihydro-2-(2,3-dimethoxyphenyl)-4-oxo-2H-1,3-thiazine-5-carbonitrile (3q)
Yellow crystals, m.p. 230-232 ℃; IR (ν/cm^{-1}): 3342(NH), 2219 (CN), 1662 (C O); 1H nmr (DMSO-*d6*): δ H = 9.20 (s, 1H, NH); 8.46 (d, J＝2.4 Hz, 1H, NH), 7.37 (t, J＝7.6 Hz, 2H, Ar- H), 7.27 (d,*J*＝7.6 Hz, 1H, Ar- H), 7.22 (t, J＝7.2 Hz, 2H, Ar- H), 7.07 (d, J＝8.0 Hz, 1H, Ar- H), 7.00 (d, J＝8.4 Hz, 1H, Ar- H), 6.95 (d, J＝8.0 Hz, 1H, Ar- H), 6.06 (d, J＝2.8 Hz, 1H, CH), 4.48 (dd, J＝16.0 Hz, 2H, CH_2); 3.75 (s, 3H,OCH_3), 3.74 (s, 3H, OCH_3), ^{13}C nmr (DMSO-*d6*): δ C = 48.04 (CH_2), 55.22 (OCH_3), 56.22 (OCH_3), 58.10 (CH), 73.99 (C5),117.06 (CN), 125.96, 127.24, 127.95,128, 05, 128.53, 129.07, 130.05, 130.21, 137.92, 138.28, 139.77, 152.21 (C-Ar), 165.51 (C O), 167.38(C6) ppm. Anal. Calcd. for $C_{20}H_{19}N_3O_3S$: : C, 62,97; H, 5,02; N, 11,02; O, 12,58; S, 8,41; Found: C, 62,98; H, 5,03; N, 11,02; O, 12,59; S, 8,42.
6-(Benzylamino)-2-(chlorophenyl)-4-oxo-5-cyano-3,4-dihydro-2H-1,3-thiazine (3r)
Pale yellow crystals, m.p. 253- 253°C; IR (ν/cm^{-1}): 3340(NH), 2216 (CN), 1662 (CO). ^{1}H nmr (DMSO-*d6*) δ H= 8.98 (t, J＝6.2 Hz *1H*, NH), 8.43 (d, J＝2.1 Hz, *1H*, NH), 7.70 (m, 5H, Ar- H), 7.22(d, J＝8.0 Hz, 2H, Ar- H), 6.62 (d, 2H, J＝8.0 Hz, CH, Ar- H), 6.89 (d, 1H, J＝2.8 Hz, CH), 4.48 (dd, J＝16.0 Hz, 2H, CH_2); ^{13}C nmr (DMSO-*d6*): δ_C = 48.49 (CH_2), 57.44 (CH), 74.43 (C5),117.33 (CN), 125.96, 127.45, 127.67, 127.90, 128,25, 128.68, 129.03, 129.43, 131.67, 134.03, 136.61, 138.22, (C-Ar), 165.77 (CO)ppm: 167.38(C6) ppm. Anal. Calcd. for $C_{18}H_{14}N_3OSCl$: C, 60.76; H, 3.97; N, 11.81; O, 4.50; S, 9.01; Cl, 9.96. Found: C, 60.75; H, 4.00; N, 11.80; O, 4.51; S, 9.03; Cl, 9.97.
2-(4-florophenyl)-3,4-dihydro-4-oxo-6-(benzyl-amino)-2H-1,3-thiazine-5-carbonitrile(3s)
Pale red crystals, m.p. 187-188 ℃; IR (ν/cm^{-1}): 3342(NH), 2222 (CN), 1660 (C O); ^{1}H nmr (DMSO-*d6*): δ H = 9.05 (t, 1H, NH), 8.34 (d, J＝3.2 Hz, *1H*, NH), 7.83 (d, *J*＝8.8 Hz, 2H, Ar- H), 7.550 (t, *J*＝8.0 Hz, *2H*, Ar- H), 7.45 (d, *J*＝8.0 Hz, 2H, Ar- H), 7.40 (t, J＝8.0 Hz, 1H, Ar- H), 7.21 (d, *J*＝7.6 Hz, *2H*, Ar- H), 6.86 (d, *J*＝3.2 Hz, *1H*, CH); 4.48 (dd, J＝16.0 Hz, *2H*, CH_2) ; ^{13}C nmr (DMSO-*d6*): δ C = 48.04 (CH_2), 58.10 (CH), 73.99 (C5),117.00 (CN), 116.16, 125.99, 127.04, 127.35, 127.47, 127.67, 128.37, 128.66, 128.53, 137.62, 138.17, 159.89 (C-Ar), 165.51 (C O), 167.38(C6) ppm. Anal. Calcd. for $C_{18}H_{14}N_3OSF$: C, 63.70, H, 4.16.; N, 12.38; O, 4,71; S, 9.45; F, 5.61. Found: C, 63.71, H, 4.17; N, 12.40; O, 4,73; S, 9.46; F, 5.62.
2-(2,5-Difluorophenyl)-3,4-dihydro-4-oxo-6-(Benzylamino)-2H-1,3-thiazine-5-carbonitrile (3t)
Redish brown crystals, m.p. 118-119 ℃; IR(ν /cm^{-1}): 3330, 3250 (NH), 2230 (CN), 1660 (C O); ^{1}H nmr (DMSO-*d6*): δ H = 9.36 (s, *1H*, NH), 8.53 (d, *J*＝3.2 Hz, *1H*,NH), 7.86 (s, 1H, Ar- H), 7.74 (s, *2H*, Ar- H), 7.47 (t, J＝ 7.6 Hz, 2H, Ar- H), 7.37 (t, *J*＝7.6 Hz, *1H*, Ar- H), 7.19 (d, *J*＝7.2 Hz, 2H, Ar- H), 6.23 (d, *J*＝3.6 Hz, *1H*, CH); 6.67 (d, *J*＝2.8 Hz, 1H, CH), 4.46 (dd, *J*＝16.0 Hz, 2H, CH_2; ^{13}C nmr (DMSO-*d6*): δ_C = 48.49 (CH_2), 57.44 (CH), 74.43 (C5),117.33 (CN), 125.96, 127.45, 127.90, 129.03, 129.43, 129.83, 131.67, 134.03, 136.61, 138.22,156.21, 158.99, (C-Ar), 165.77 (C O), 167.38(C6) ppm. Anal. Calcd. for $C_{18}H_{13}N_3OSF_2$; C, 60.49; H, 3.67; N, 11.76; O, 4,48; S, 8.97; F, 10.63. Found: C, 60.50; H, 3.69; N, 11.77; O, 4,50; S, 8.98; F, 10.65.

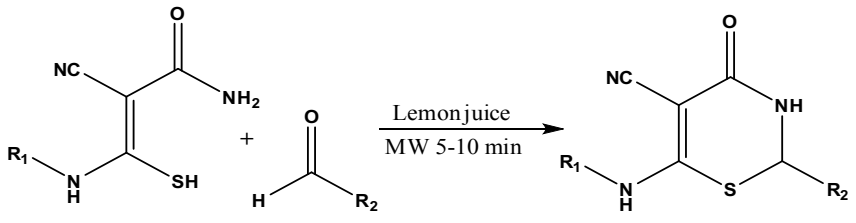
2.3. Antifungal activity
Antifungal activity of the synthesized products was evaluated against each of the following pathogenic fungi: *Aspergillus niger, Fusarium oxysporum, Verticillium dahlia, and Aspergillus flavus* by the poison plate technique. After dissolving each test compound in 10 ml of diethyl ether and mixing with 90 ml of potato dextrose agar (PDA), the concentrations of were calculated to 100 µg/ml. For antifungal assay, the four types of fungi were incubated in PDA for 3-4 days at 25 °C for appreciable growth of mycelium before cutting mycelia disks of 0.5 cm diameter from the culture medium with sterilized inoculation needles. The disks were then inoculated in the PDA plates. After inoculation, all plates were incubated for 5 days at 25 °C. The control samples in this study were made of diethyl ether in distilled water and the standards used, as for all treatment, were clotrimazole and amphotericin-B performing 3 replicates in each case. Radial growth of the fungal colonies was evaluated after 4 days of growth where the data were statistically analyzed.

3. Results and discussion

3.1 Chemistry

Recently, It has been reported that 3-arylamino-2-cyno-3-mercaptoacrylamides 1 reacted with various of aromatic aldehydes 2 in ethanol catalyzed by lemon juice [25]. The reaction proceeded to yield mainly one single product 3. However, when using the previous conditions aromatic aldehydes 2 did not react smoothly with 3-arylamino-2-cyno-3-mercaptoacrylamides 1. Low yields of compound 3 were obtained schem1.

In continuation of our research work to develop sustainable methodologies for the synthesis of biologically active heterogeneous ring scaffolds , we present here the synthesis of 2,3-dihydro-1,3-thiazin-4(1*H*)-one derivatives 3 by using lemon juice as a natural biodegradable catalyst under microwave irradiation. Achieving an optimized reaction yield and favorable conditions, we irradiated the reaction mixture of many of aromatic aldehydes 2 and 1 using lemon juice as solvent and as a natural catalyst. Fortunately, the reactions proceeded to give compounds 3a–t after few minutes in good yields (70–96%)



1 2 **Schem 1** 3a-t

In the present investigation, we have study effect compounds 3a–n having aryl groups with electron donating and -withdrawing substituents on the benzene ring to examine their effect on reaction. The yield is lower in case of electron-withdrawing substituents as the yield in the p-nitro group decreased the yield to 70%. From other hand, the yield higher in case of electron-donating substituents as the yield in 3,4-dimethoxy substituent of **3q** reached 96%. (See Table 1).

Table1: 6-Arylamino-5- cyano-2,3-dihydro-1, 3-thiazin-4(1H)-ones 3a-t

Compound	R_1	R_2	T/min	Y%
3a	Ph-	Phenyl	8	74
3b	Ph-	4-Tolyl	9	77
3c	Ph-	4- Methoxyphenyl	9	96
3d	Ph-	2,3-Dimethoxyphnyl	9	80
3e	Ph-	3,4-Dimethoxyphnyl	9	83
3f	Ph-	4-Chlorophenyl	5	78
3g	Ph-	4-Nitrophenyl	10	70
3h	Ph-	2,4- Dichlorophenyl-	10	72
3i	Ph-	4-Bromophenyl	5	87
3j	Ph-	Cyclohexyl	6	80
3k	Ph-	1-Naphtyhl	8	83
3l	Ph-CH_2	1-Naphtyhl	9	88
3m	PhCH_2	Phenyl	7	78
3n	PhCH_2	4- Tolyl	9	70
3o	Ph-CH_2	4- Methoxyphenyl	7	72
3p	Ph-CH_2	3, 4-Dichlorophenyl-	9	71
3q	Ph-CH_2	3,4-Dimethoxyphnyl-	6	96
3r	Ph-CH_2	2(4-Chlorophenyl-)	5	80
3s	Ph-CH_2	4-Flourophenyl	9	70
3t	Ph-CH_2	2,5-Diflourophenyl	10	70

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 3a-t by using lemon juice as a natural acid catalyst under microwave irradiation method. Many of the reported synthetic methods were 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. 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 3a-t. This reaction proceeds by condensation of 3-arylamino-2-cyano-3-mercaptoacrylamides 1 with various of aldehydes 2 applying Lemon juice as a natural acid catalyst and solvent under microwave irritations. The efficiency of the methodology towards various substituted aldehydes is very good viz. fast reaction rate and the excellent yield.

3.2 Antifungal activity

The antifungal activity of some synthesized compounds 3a-t was tested against four pathogenic fun gi, *Fusarium oxysporum, Aspergillus niger, verticillium dahliae and and Aspergillus flavus,* as shown table (2).

Table (2) Antifungal activity of some synthesized compounds 3a-t**.**

Compd (100 ug)	*Fusarium oxysporum*	*Aspergillus niger*	*verticillium dahliae*	*Aspergillus flavus*
3a	-	-	-	-
3c	10.9	12.8	-	-
3f	12.8	10..9	-	-
3g	10..9	14.5	-	-
3l	5.2	4.9	-	3.8
3m	14.5	15.9	--	12.4
3n	16.7	14.6	--	14.6
3o	17.6	13.9	12.5	13.7
3p	19.1	17.3	14.7	14.6
3q	17.9	16.9	15.8	14.9
3r	18.5	12.8	14.1	16.7
3s	16.7	11.8	16.6	15.8
3t	26.6	15.2	17.8	16.5
St. Drugs	24	24	26	28

Most of synthesized compounds showed moderate activity against the tested fungal strains. Compounds 3p, 3r with Chloro substitution on ring showed excellent activity against *F. oxysporum* (19.1-18.5 mm) whereas compounds 3o, 3q with methoxy substitution on ring were very good active against the same strain (17.6, 17.9 mm) Compound 3t (26.6 mm) tested against *F. oxysporum* showed maximum zone of inhibition than standard drug Clotrimazol. Furthermore compounds 3p, 3q showed good activity against *A. niger* (17.3, 16.9), whereas compounds 3r, 3s showed very good activity against *A. flavus* (16.7 , 15.8 mm).Moreover compounds 3p, 3r chloro substitution on ring showed good activity against *V. dahliae(* 14.7, 14.1 mm*)* Finally compounds 3s, 3t with fluoro substitution on ring showed maximum activity against *V. dahliae* (16.6, 17.8 mm) and compounds 3o, 3q with methoxy substitution on ring were found to be active against *V. dahliae* (12.5, 15.8 mm), The remained compounds displayed negative effect against *V. dahlia*e.

Conclusion

we report in this study that 3-arylamino-2-cyno-3-mercaptoacrylamides 1 reacted with various of aromatic aldehydes 2 using lemon juice as a natural catalyst and solvent under microwave irradiation to produce 6-arylamino-5-cyano-2,3-dihydro-1,3-thiazin-4(1H)-ones 3 in good yields. The advantages of the reported method are as follow: available starting materials, short reaction time (min), simple work-up, environment friendly and appreciable yields of reactions. The study also showed the activity of these antifungal pathogens for plants, which suggests the possibility of using and developing these compounds to be used as fungicides to treat many diseases of plants.

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