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ULTRASONIC ASSISTED SYNTHESIS AND OPTIMIZATION OF 2-AMINO-4H-CHROMENE'S DERIVATIVES

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ABSTRACT: A one pot three component reaction of 2-amino-4-aryl-4*H*-chromene and its derivatives were synthesized under ultrasonic irradation using morpholine as a catalyst in aqueous condition. The synthesized titled derivatives were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectra and elemental analysis. When compared to traditional method, ultrasonic irradiation is a morden technology for improving prepared in higher yields, shorter reaction time and mild condition.

KEYWORDS: 2-amino-4-aryl-4*H*-chromene, Morpholine, Ultrasound irradiation, one pot three component reaction,aqueous condition.

INTRODUCTION:

The expansion of the chemical industry has been a major feature of the twenty-first century, resulting in significant improvements in living standards. One of humanity's greatest achievements is the production of organic pharmaceutical compounds, which play a crucial function in the biological system[i]. Solvents, toxic chemicals, hazardous substances, energy-intensive processes, and waste generation are among the chemicals necessary for the development of novel compounds. The entire planet is beset by major environmental issues. As a result, chemical and pharmaceutical industries have used green chemistry practices to synthesize novel chemical moiety in recent decades[ii]. Because hazardous metals are typically poisonous and difficult to dispose of correctly in large quantities, avoiding and minimizing their use in chemical processes is an important aspect of this invention. Furthermore, the highly poisonous and hazardous volatile nature of many organic solvents poses a substantial environmental threat because they contribute significantly to chemical waste. As a result, it is critical to employ less dangerous and environmentally friendly processes when synthesizing new chemical compounds[iii].Green synthesis can be done in a variety of ways, including bio based techniques, microwave, ultrasonic irradiation, plants and phytochemicals, enzymes, and vitamins, among others. One-pot multicomponent reactions are a new approach for creating or breaking bonds in heterocyclic compounds with great atom economy, and the diversity can be obtained by altering the reacting components. Higher yields, shorter reaction times, and softer

conditions were obtained by carrying out a large number of organic reactions[iv-vi]. The use of ultrasound effects for doing chemical reactions is called sonochemistry[vii]. Water is now used as a green solvent in numerous reactions since it is environmentally friendly and produces high yields. Water is less expensive and simple to use, and it gives MCRs a target moiety[viii]. Chromene-containing heterocycles have intriguing properties that make them a desirable target for MCRs. Many oxygen-containing heterocyclic natural compounds include the 4*H*-chromene molecule, and its pharmacological and biological characteristics have long been recognised[ix] .

2-amino-4-aryl-4H-chromene are a kind of heterocyclic chemical with a wide range of biological applications.Antimicrobial[x], antiviral[xi], mutagenicity[xii], antiproliferative[xiii], sex hormone[xiv], antitumor[xv], cancer therapy[xvi],and central nervous system activity[xvii] are only a few of the pharmacological activities that such compounds have demonstrated in recent years.

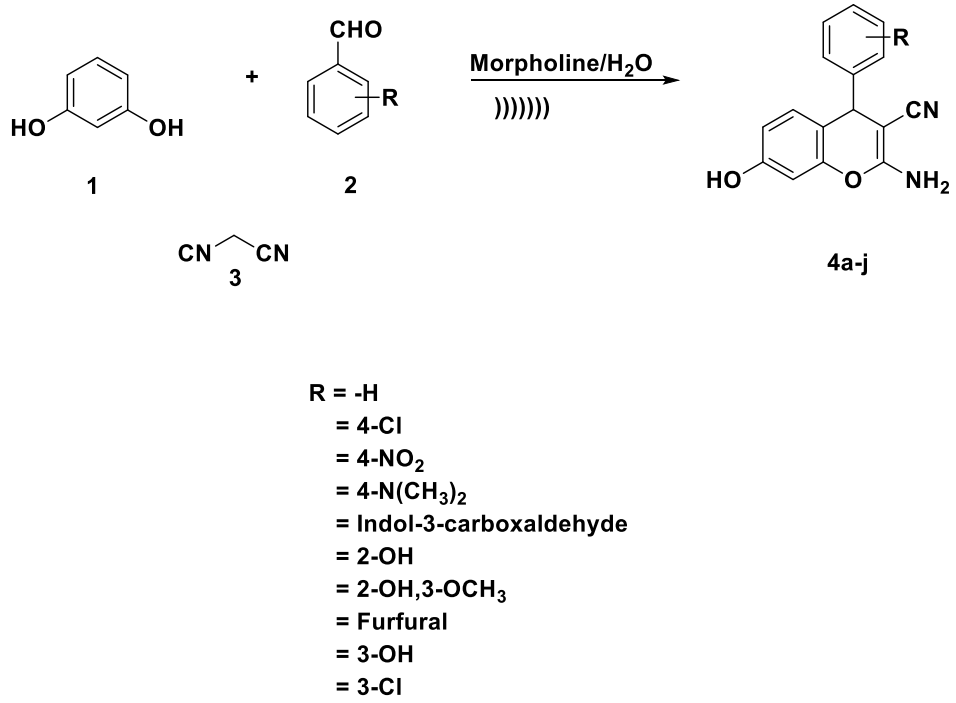
EXPERIMENTAL:

The reagents and solvents required for synthesis were purchased from Merck ltd., sdfine chemicals and LOBA chemie. The melting points of the final derivatives were determined by open-end capillary method and were reported uncorrected. TLC plates purchased from Merck (TLC silica gel 60 F_{254}) and mixture of n-hexane: ethyl acetate (6:4) was used as mobile phase. The IR spectra for each derivative were collected using Bruker FT-IR alpha-t (ATR). ^{1}H NMR and ^{13}C NMR data were obtained using Bruker spectrometer-400MHz and 100MHz respectively (DMSO-d_6 was used as solvent and TMS as reference). Mass spectra data for each derivative was determined using Schmindzu mass spectrophotometer. Perkin-Elmer 2400 CHN analyzer was used to procure elemental data.

GENERAL PROCEDURE:

ultrasound irradiation for the synthesis of 2-amino-4-aryl-4H-chromene and its derivatives.

A mixture of resorcinol (1 g, 9 mmol), malononitrile (0.59 g, 9 mmol) and substituted aldehyde (9 mmol) in water (5 ml) with catalytic amount of Morpholine (0.043 gm , 5 mmol) was irradiated by an ultrasonic irradiation (33 kHz) at room temperature (30 °C). The completion of reaction was monitored periodically by TLC using n-hexane: ethyl acetate (60:40 v/v) as mobile phase. The obtained product was filtered, washed with water (5 mL), dried and recrystallized from ethanol.



Scheme 1.

ANALYTICAL DISCUSSION:

Synthesis of 2-amino-7-hydroxy-4-Phenyl-4*H* Chromene -3 carbonitrile (4a)
IR(ATR): 3642, 3335, 3224, 2190, 1659, 1580 cm^{-1}.^{1}H NMR(400 MHz,DMSO-d_6, δ, ppm): δ=4.58 (s, 1H, H-4), 6.46 (s, 2H, NH_2), 6.72-7.30 (m, 8H, Ar-H), 9.60 (s, 1H, OH). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ= 56.3, 102.2, 112.2, 113.4, 120.5, 122.4, 127.3, 128.3, 129.6, 146.1, 148.8, 156.9, 160.1. MS (m/z): 265 M^+. m.p.: 200-215°C; Yield: 88 %; Anal. Calcd. For $C_{16}H_{12}N_2O_2$ (264): C, 72.72; H, 4.58; N, 10.60%. Found C, 72.43; H, 4.36; N, 10.49%.

Synthesis of 2-amino-4-(4-chloro-phenyl)-7-hydroxy-4*H* Chromene -3 carbonitrile (4b)
IR (ATR): 3642, 3335, 3224, 2190, 1659, 1580 cm^{-1} .^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): δ = 4.72 (s, 1H, H-4), 6.97 (s, 2H, NH2), 6.39-7.31 (m, 7H, Ar-H), 9.70 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ = 56.1, 102.7, 112.8, 113.3, 120.9, 128.5, 129.7, 130.5, 146.0, 149.3, 157.9, 160.8. MS (m/z): 299 M^+. m.p.: 90-95°C; Yield: 82 %; Anal. Calcd. For $C_{16}H_{11}ClN_2O_2$ (298.05): C, 64.33; H, 3.71; N, 9.38%. Found C, 64.32; H, 3.62; N, 9.32%.

Synthesis of 2-amino-7-hydroxy-4(4-nitro-phenyl)-4*H* chromene 3- carbonitrile (4c)
IR (ATR): 3642,3335, 3224, 2190, 1659, 1580, 1575 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6, δ,ppm): δ=4.72 (s, 1H ,H-4),6.97(s,2H,NH_2), 6.39-7.31 (m, 7H, Ar-H), 9.70 (s, 1H, OH).^{13}C NMR (100 MHz,DMSO-d_6, δ,ppm): δ= 56.1, 102.7, 112.8, 113.3, 120.9, 128.5, 129.7, 130.5,146.0, 149.3, 157.9,160.8.; MS (m/z): 310 M^+, m.p.: 90-100°C; Yield: 87 %; Anal. Calcd. For $C_{16}H_{11}N_3O_4$: (309) C-64.33, H, 3.71; N, 12.78%.; Found: C-64.32, H-3.59, N-l2.38%.

Synthesis of 2-amino-4(4-dimethylamino-phenyl)-7hydroxy-4*H* chromene 3- carbonitrile (4d)
IR (ATR):1516, 1680, 2198, 3250, 3440 cm^{-1}.^{1}H NMR (400 MHz,DMSO-d_6, δ,ppm): δ=3.10(s,6H,-CH_3,N,N-dimethyl grop),4.72 (s,1H,H-4),6.72 (s,2H,NH_2),6.24-7.26 (m,7H,Ar-H),9.70 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ =29.4, 41.3, 59.2, 102.7,

110.4, 112.9, 113.6, 117.5, 129.3, 130.5, 148.5, 155.5, 158.0, 177.1. MS (m/z): 308 M^+ .m.p.: 180-190°C; Yield: 88 %; Anal. Calcd. for $C_{18}H_{17}N_3O_2$ (307): C-70.34, H-5.58, N-13.67; Found: C-69.29, H-4.74 , N-12.79%.

Synthesis of 2-amino-7-hydroxy -4-(1*H*-indol-7-yl)-4*H* chromene 3- carbonitrile (4e)
IR (ATR): 3590, 3422, 3330, 2193, 1652, 1578 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ,ppm): δ= 4.94 (s,1H ,H-4),6.85 (s,2H,NH_2),6.35-7.98 (m ,7H, Ar-H), 7.1 (d, 1H, indonyl-H),9.85 (s,1H,OH), 10.81 (s, 1H, indonyl-NH).^{13}C NMR (100 MHz,DMSO-d_6, δ, ppm):δ =56.8, 112.2, 116.7, 118.8, 119.3, 121.6, 128.3, 129.7, 137.9, 149.1, 160.4. MS (m/z): 304 M^+. m.p.: 160-165°C; Yield: 83 %; Anal. Calcd. for $C_{18}H_{13}N_3O_2$ (303.10): C, 71.28; H, 4.32; N, 13.85%. Found: C, 70.97; H, 4.28; N, 13.81%.

Synthesis of 2-amino-7-hydroxy-4-(2-hydroxy-phenyl)-4*H* chromene 3- carbonitrile (4f)
IR (ATR): 3628, 3336, 3228, 2189, 1653, 1583 cm^{-1}.^1H NMR (400MHz,DMSO-d_6, δ,ppm): δ = 4.48 (s,1H ,H-4), 6.83 (s, 2H,NH_2),6.38-7.15 (m,7H,Ar-H), 9.32 (s,1H ,OH), 9.69 (s, 1H , 7-OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm):δ = 56.9, 102.5, 112.8, 114.3, 121.0,128.7,129.9, 130.4, 149.3, 157.3, 158.4, 160.6.MS (m/z): 281 M^+.m.p.: 90-95°C; Yield:90 %; Anal. Calcd. for $C_{16}H_{12}N_2O_3$ (280): C, 68.57; H, 4.32; N, 9.99%. Found C, 68.53; H, 4.28; N, 9.95%.

Synthesis of 2-amino-7-hydroxy-4-(4-hydroxy-3-methoxy-phenyl)-4*H* chromene 3-carbonitrile (4g)
IR (ATR): 1583, 1653,2189,3628, 3336, 3228, cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): δ = 4.48 (s, 1H, H-4), 2.04(s, 2H, NH2), 6.38-7.15 (m, 6H, Ar-H), 3.75 (s, 1H, OCH3), 5.69(s, 1H, 7-OH), 5.69 (s, 1H, 7-OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ = 29.7,56.3,104.7,110.4,117.2,122.1,124.1,136.6,140.4,149.7,158.0,177.1,177.2,MS (m/z): 311 M^+.m.p.:80-85°C; Yield: 85 %; $C_{17}H_{14}N_2O_4$(310): C-60.20;H-4.71; N-8.75; Found: C-60.29; H-4.74;N-8.79%.

Synthesis of 2-amino-4-furan-2yl-7-hydroxy-4*H*-chromene 3-carbonitrile (4h)
IR (ATR): 3615, 3415, 3385, 2192, 1651, 1587 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): δ = 4.75 (s, 1H, H-4), 6.94 (s, 2H, NH2), 6.13 (d, 1H, J = 2, Ar-H), 6.35 (dd, 1H, J=2,J = 8, Ar-H), 6.53 (d, 1H, J = 8, Ar-H), 7.27-7.52 (m, 3H, furyl-H), 9.75 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ = 53.8, 56.0, 102.5, 106.1, 110.3, 112.4, 112.7, 120.8, 129.9,149.5, 156.9, 157.7, 161.1. MS (m/z): 254 M^+ m.p.: 190-200°C; Yield: 81%; Anal. Calcd. For $C_{14}H_9N_2O_3$(253) : C, 66.14; H, 3.96; N, 11.02%. Found C, 66.04; H, 3.90; N, 10.97%.

Synthesis of 2-amino-7-hydroxy-4-3(hydroxy-phenyl)-4*H*-chromene 3-carbonitrile (4i)
IR (ATR): 3629, 3336, 3230, 2188, 1651, 1585 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): δ = 4.49 (s, 1H, H-4), 6.85 (s, 2H, NH2), 6.39-7.08 (m, 7H, Ar-H), 9.33 (s, 1H, OH), 9.68 (s, 1H, 7-OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ = 57.1, 102.6, 112.9, 114.4, 121.2, 128.9, 129.9, 130.4, 149.2, 157.4, 158.4, 160.5. MS (m/z): 281 M^+. m.p.: 160-165°C; Yield: 98 %; Anal. Calcd. For $C_{16}H_{12}N_2O_3$ (280): C, 68.57; H, 4.32; N, 9.99%. Found C, 68.52; H, 4.25; N, 9.96%.

Synthesis of 2-amino-4(3-chloro-phenyl) 7-hydroxy-4*H*-chromene 3-carbonitrile (4j)
IR (ATR): 3639, 3338, 3220, 2192, 1655, 1582 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): δ = 4.73 (s, 1H, H-4), 6.94 (s, 2H, NH2), 6.37-7.30 (m, 7H, Ar-H), 9.73 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): δ = 56.3, 102.6, 112.9, 113.4, 121.1, 128.3, 129.6, 130.3, 145.8,

149.1, 157.7, 160.7. MS (m/z): 299.5 M^+. m.p.: 70-80°C; Yield: 88 %; Anal. Calcd. For $C_{16}H_{11}ClN_2O_2$ (298): C, 64.33; H, 3.71; N, 9.38%. Found C, 64.31; H, 3.67; N, 9.31%.

RESULT AND DISCUSSION:

Comparison of solvents

2-amino-4-aryl-4*H*-chromene and its derivatives synthesized using Resorcinol, Malononitrile and different aldehyde 1:1:1 stocheometric ratio.Morpholine is used 5mmol and water used as a green catalyst. This reaction going on under ultrasound irradiation method. A reaction was designed as a model in order to find out the optimum solvent in Table no.1

Table 1. Comparison of solvents for the reaction of resorcinol 1, malononitrile 2, and 3-hydroxy benzaldehyde to afford 2-amino-7-hydroxy - 4-3(hydroxy phenyl) - 4*H*-chromene-3-carbonitriles (4i)

No.	Solvent	Time (min)	Yield %
1	Solvent free	05	None
2	Water	03	98
3	Ethanol	05	80
4	Methanol	05	78
5	Acetone	09	62
6	n-Hexane	17	65
7	Toluene	20	-

Comparison of ultrasonic irradiation and conventional methods:

Ultrasound irradiation is a type of irradiation that uses high-frequency sound to determine the specific effect of ultrasound on this reaction. When the reaction was carried out using the traditional approach, it yielded relatively poor product yields and took longer to complete, but the identical reaction carried out under the effect of ultrasonic irradiation yielded outstanding product yields in a fast reaction time. Thus, ultrasonic irradiation was found to be superior to the old technique in terms of yield, reagents, and yield of 2-amino-4-aryl-4*H*-chromene derivatives.

Table 2. Synthesis of 2-amino-4-Phenyl-4*H*-chromene 2 derivatives under sonication and conventional conditions.

No.	Compound	- R	Ultrasonic irradiation		Conventional method	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1	4a	-H	02	88	120	50
2	4b	4-Cl	04	82	180	47
3	4c	4-NO_2	05	87	120	54
4	4d	4-$N(CH_3)_2$	05	88	90	41
5	4e	Indol-3-Carboxaldehyde	06	83	110	50
6	4f	2-OH	04	90	180	50
7	4g	2-OH,3-OCH_3	05	85	120	34
8	4h	Furfural	06	81	180	45
9	4i	3-OH	03	98	150	54
10	4j	3-Cl	04	88	90	40

Table 3. Effect of amount of catalyst in the synthesis of the product 4i

No.	Amount of morpholine (equiv %)	Time (min)	Yield %
1	Trace	02	Trace
2	5	03	98
3	10	04	90
4	15	06	89
5	20	05	87
6	25	05	87
7	30	06	85

Table 4. Effect of Time in the synthesis of the product 4i

No.	Solvent	Time (min)	Yield %
1	Water	03	98
2	Water	05	92
3	Water	10	92
4	Water	15	90
5	Water	20	89

Table 5. Effect of Temperature in the synthesis of the product 4i

No.	Solvent	Temperature (^{0}c)	Time (min)	Yield %
1	Water	30	03	98
2	Water	40	05	88
3	Water	50	05	82
4	Water	60	06	81
5	Water	70	06	80

CONCLUSION:

We have developed a green technique for the synthesis of 2-amino 4-aryl-4*H*-chromene derivatives by employing water as a green solvent in a one-pot multicomponent reaction under ultrasonic irradiation. This approach has a number of advantages, including greater product yields, a faster reaction time, and simple set-up. We can observe a comparison between green and traditional methods in this research. Finally, the green approach produces a high yield in a short period. This result indicated that optimization studies, which provides information on various solvents, time, temperature, and base quantity, among other things. Finally, we conclude that employing water as a solvent in this method is the best way to produce the best results.

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