Heterocyclic Letters
Vol. 13| No.3|573-582|May-July|2023
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

ULTRASOUND ASSISTED SYNTHESIS AND CHARACTERIZATION OF CARBONITRILE BEARING PYRAN DERIVATIVES AND IT'S ANTIMICROBIAL ACTIVITY

Prakashbhai V. Bishnoi [a*], Jasmin H. Kumbhani [b] and Parimal M. Chatrabhuji [a]

[a] *Pramukh Swami Science & H D Patel Arts College, Kadi-382715, Gujarat, India*
[b] *M B Patel Science College, Anand, S P University, VV Nagar-388001, Gujarat, India*
**Correspondence: bishnoichemistry@gmail.com*

Abstract: Carbonitrile-containing pyran derivatives with an electron-withdrawing substituent (-R) were produced via a one-pot, three-component procedure including a cyclization reaction between malononitrile, diketone, and variously substituted aldehydes with morpholine as a catalyst in aqueous condition in ultrasonic irradiation. By FTIR, ^{1}H NMR, ^{13}C NMR, MASS Spectra, and elemental analyses, the structural development of named derivatives was verified.

Keywords: 4*H*-pyran, ultrasonic irradiation, dimedone, synthesis, antimicrobial activity.

Introduction: 4*H*-pyrans are a highly beneficial class of oxygen-containing heterocyclic chemicals that are abundant in natural products such as fruits and vegetables. As medicinal molecules, 4*H*-pyran possesses many biological and pharmacological actions, including antimicrobial, antibacterial, antifungal, antiviral, antioxidant, antileishmanial, antiallergenic, hypotensive, anticoagulant, and diuretic activity. Typically, as a component of 4H-chromene derivatives, recent research suggests that molecules with a 4*H*-pyran core are effective in the treatment of Alzheimer's, schizophrenia, and myoclonus. Additionally, 4*H*-pyrans have been used as calcium channel blockers. This class of organic compounds is being used in the cosmetic and agrochemical industries. [i-v]

There are traditionally two kinds of catalysts, homogeneous and heterogeneous. Homogeneous catalyst facilitates the accessibility of active centers to the reactant, resulting in a catalyst with high activity. While heterogeneous catalyst has a distinct phase from the reactant. Heterogeneous catalysts are often less active than homogeneous catalysts because the active sites in heterogeneous catalysts are not as readily accessible as in homogeneous systems. Other benefits of the homogeneous catalytic system include strong selectivity, good turnover frequency (TOF), good turnover number (TON), high activity, and good selectivity.[xx]

Historically, the reaction has been carried out using a variety of basic reagents or catalysts, including NaOH, Ba $(OH)_2$, and Mg-Al-O-tBu hydrotalcite. Frequent side reactions under high basic conditions include aldol or self-aldol addition, polymerizations, retrogressions, and rearrangements.[vi-x] Various Lewis and Bronsted acid catalysts, such as $CuBr_2$, $InBr_3$, $[Al(DS)_3.3H_2O$, Au(III), $CeCl_3.7H_2O$–NaI,SmI_3, and K10–FeO, as well as metal salts, have been utilised to catalyse Michael reaction in recent years. The disadvantages of this sort of

catalyst, however, include acidic conditions, costlier reagents, a longer reaction time, and a reduced product yield. [v]

The number of reactions and purification steps in multi-step synthetic procedures, as well as harsh reaction conditions and long work-ups, result in the creation of significant quantities of hazardous waste. Are among the most significant requirements for the process's efficiency and practicability and should be as little as feasible. Therefore, academic and industrial research has progressively highlighted the use of MCRs and domino reaction sequences for a wide variety of products during the last decade. The development of an effective catalytic system for the synthesis of 4*H*-pyrans is the focus of a substantial amount of research. [vi]

Multicomponent reactions (MCRs) are a versatile and potent technique in contemporary synthetic organic chemistry, allowing for the simple formation of several new bonds in one-pot processes. [xv,xvi] Thus, the synthesis of 4H-pyran by multicomponent reactions with an appropriate catalyst might increase their ecological efficiency. Several types of catalysts, including acetic acid, [xvii] carbonaceous material (C-SO_3H), p- TSA, and L-Proline, have been employed to accelerate MCR (multicomponent reaction)-based processes. [xx]

Multicomponent reactions (MCRs) have evolved as efficient chemical processes. Clearly, the benefits of the current chemical reaction include a simple, rapid, efficient, and environmentally friendly purification approach as well as high product yields. "Today, the efficiency of a chemical synthesis may be judged not only by selectivity and total yield, but also by its raw material, time, human resources, and energy needs, as well as the toxicity and dangers of the chemicals and the procedures involved." [x]

The difficult issue of establishing a simple, environmentally friendly, and cost-effective reaction method for medicinal chemistry is a significant field of both academic and pharmaceutical research. Multicomponent reactions (MCRs), start with basic components in what could be one of the most advantageous procedures in synthetic chemistry. [viii,vix]

Developing MCR processes in aqueous medium is an active field of study in this direction that has several benefits, including the absence of carcinogenic effects, decreased pollution, lower cost, and ease of processing, which are beneficial to both the industry and the environment. [xviii]

Today, the emphasis of chemical synthesis is on developing novel synthetic methods that adhere to the principles of green chemistry. This has received a great deal of attention owing to rising environmental contamination concerns. The advancement of green chemistry relies heavily on catalysis and green solvents, namely water. Recent research has proved the significance of H_2O or aqueous media for chemical processes, as a result of the toxicity of organic solvents, which has led to the invention of novel ways for using H_2O as a solvent. [xiii]

On the other hand, the application of ultrasonic irradiation produces very effective green chemical treatments from an economic and synthetic standpoint.[v] Ultrasonic irradiation speeds organic synthesis at ambient temperature and pressure without the need for high temperature and pressure. [vi] Sonochemical reactions are advantageous due to their ease, safety, high product purity, adjustable reaction conditions, and increased catalytic efficiency. Sonochemistry is included among the most favoured environmentally friendly chemical processes due to its unique qualities. [xxii]

"The contact between molecules and ultrasound is not direct, but the energy of these long wavelengths may induce cavitation, therefore accelerating the process". [vii]

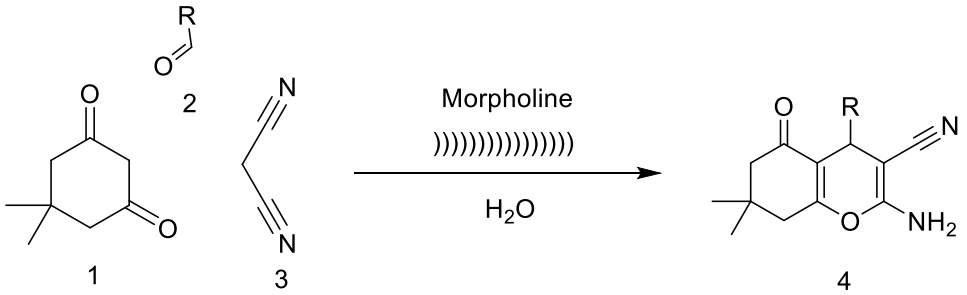
Due to these distinctive characteristics, we anticipate that this technology will be exploited in the creation of 4*H*-pyrans analogues. In our laboratory, the potential bioactivity of the structures is now being investigated. [xxii]

Either ultrasonic or microwave-assisted synthesis of diverse organic compounds in the presence or absence of catalysts considerably increased reaction rate, decreased reaction

durations, decreased energy consumption, increased selectivity, and increased product yield. Compared to traditional procedures, these protocols have shown to be effective, quick, clean, environmentally friendly, and consistent in chemical labs. Sonochemistry, one of the frontier fields in organic synthesis, has significant promise for the energy-efficient enhancement of reaction speeds due to the automated effects of sound waves (heterogeneous processes) and chemical initiation (homogeneous processes). Typically, responses induced by ultrasonic irradiation are simpler to manipulate than those induced by traditional means. Due to our interest in the synthesis of heterocyclic molecules with possible biological activity, we were motivated by these findings.[xvi-xxii]

EXPERIMENTAL SECTION

The reagents and solvents required for synthesis were purchased from Spectrochem, Merck ltd., SDfine Chemicals and LOBA. The melting points (M.P) of the final derivatives were determined by open-end capillary method. TLC plates purchased from Merck (TLC silica gel 60 F_{254}) and mixture of ethyl acetate: n-hexane (4:6) was used as mobile phase. The FTIR spectra for each derivative were collected using Bruker FT-IR alpha-I (ATR). ^{1}H NMR and ^{13}C NMR data were obtained using Bruker spectrometer-400MHz and 100MHz respectively (DMSO-d6 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.



R = C_6H_5
= 4-Cl-C_6H_4
= 4-NO_2-C_6H_4
= 4-$N(CH_3)_2$-C_6H_4
= 2-OH-C_6H_4
= 2OH, 3OCH_3-C_6H_3
= Furfural
= 3-OH-C_6H_4
= 3-Cl-C_6H_4
= 4-OH-C_6H_4

Scheme 1 Common Synthesis of 4H Pyran

GENERAL PROCEDURE:

A mixture of dimedone (7mmol), malononitrile (7 mmol), and substituted aldehyde (7 mmol) in water (10 ml) with catalytic amount of Morpholine (5 mmol) was irradiated by an ultrasonic irradiation (33 kHz) at room temperature (30 ^{0}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, dried and recrystallized from ethanol.

Recrystallizing have been done in presence of methanol. The structure of the products was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR spectra and mass spectrometry and comparison with authentic samples prepared using the methods described.

ANALYTICAL DISCUSSION:

Synthesis of 2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (1).

FTIR(ATR): 3389, 3318, 3203,2962,2880,2195, 1662,1600, 1366, 1210 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=0.97 (s, 3H), 1.05 (s, 3H), 2.12 (d, 1H), 2.27 (d, 1H), 2.46–2.58 (m, 2H), 4.18 (s, 1H), 7.02 (bs, 2H), 7.14–7.21 (m, 3H), 7.28–7.32 (m, 2H) ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=38.6, 51.5, 58.1, 113.9, 119.1, 127.7, 144.1, 155, 159.2, 198.9. MS (m/z): 294.14 (100.0%), 295.14 (19.5%) 296.14 (1.8%) m.p.: 227°C; Yield: 92.4 %; Anal. Calcd. For $C_{18}H_{18}N_2O_2$ (294): C, 73.46; H, 6.12; N, 9.52, O, 10.88%. Found C, 73.46; H, 6.12; N, 9.52, O, 10.88%.

Synthesis of 2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (2)

FTIR(ATR): 3374, 3174, 2955,2879,2183, 1671,1631, 1587, 1481,1359,1209,1140 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.0 (s, 3H), 1.05 (s, 3H), 2.29 (d, 1H), 2.27 (d, 1H), 2.46–2.58 (m, 2H), 4.29 (s, 1H), 7.28-7.40 (bs, 2H), 7.12–7.16 (m, 2H) ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=39.6, 58.1, 113.9, 119.1, 125.7,127.7, 130.4, 144.1, 155, 159.2, 198.9. MS (m/z): 328.10 (100.0%), 330.09 (32.0%) 329.10 (19.5%), 331.10 (6.2%), 330.10 (1.8%). m.p.: 190°C; Yield: 83.80 %; Anal. Calcd. For $C_{18}H_{17}ClN_2O_2$ (328.10): C; 65.75, H; 5.21, Cl;10.78; N,8.52%; O, 9.73%. Found C; 65.75, H; 5.21, Cl;10.78; N,8.52%; O, 9.73%.

Synthesis of 2-Amino-4-(3-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (3).

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.07 (s, 3H), 1.13 (s, 3H), 2.07 (d, 1H), 2.20 (d, 1H), 2.35–2.45 (m, 2H), 4.29 (s, 1H), 5.5(s, 1H), 6.6 (s, 1H), 6.74 (d, 1H), 7.36 (t, 1H), 7.45 (m, 1H), 7.43 (m, 1H),9.97(s, 1H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=39.7, 58.1, 113.9, 114.7, 119.1, 120.3, 127.7, 130.4, 144.1, 155, 159.2, 198.9. MS (m/z): 310.13 (100.0%), 311.14.09 (19.5%), 312.14 (1.8%). FTIR (ATR): 3306,2880,2187, 1648,1586, 1454, 1359,1249,1208,1148 cm^{-1} m.p.: 235°C; Yield: 71.82 %; Anal. Calcd. For $C_{18}H_{18}N_2O_3$ (310.35): C, 69.66; H, 5.85; N, 9.03, O, 15.47%. Found C, 69.66; H, 5.85; N, 9.03, O, 15.47%.

Synthesis of 2-Amino-4-(4-Nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4).

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.06 (s, 3H), 1.14 (s, 3H), 1.82 (d, 1H), 2.29 (d, 1H), 4.29 (s, 1H), 4.29(s, 1H), 7.52 (d, 1H), (t, 2H), 8.13(d, 2H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=27.5, 32.3, 38.6, 39.4, 51.5, 58.1, 113.9, 114.7, 119.1, 123.8, 126.9, 144.1, 155, 159.2, 198.9. MS (m/z): 339.12 (100.0%), 340.13. (1.8%), 340.12 (1.1%). FTIR (ATR): 3736, 3314, 2965, 2884, 2186, 1661, 1593, 1509, 1339,1210,1146,1034 cm^{-1} m.p.: 178°C; Yield: 85.12 %; Anal. Calcd. For $C_{18}H_{17}N_3O_4$ (339.35): C, 63.71; H, 5.05; N, 12.38, O, 18.86%. Found C, 63.71; H, 5.05; N, 12.38, O, 18.86%.

Synthesis of 2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (5).

^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.06 (s, 3H), 1.12 (s, 3H), 1.82 (d, 1H), 2.29 (d, 1H), 4.29 (s, 1H), 6.82 (s, 1H), 7.06 (d, 1H), 7.32 (t, 1H), 7.38 (m, 1H), 7.62 (m, 1H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=27.5, 32.3, 38.6, 38.9, 51.5, 58.1, 113.9, 114.7, 119.1, 120.3, 127.7, 130.4, 144.1, 155, 159.2, 198.9. MS (m/z): 328.10 (100.0%), 330.09(32.0%), 329.10 (19.5%), 331.10 (6.02%), 330.10 (1.8%) FTIR (ATR): 3306, 3157, 2971, 2881,2305, 2183, 1647, 1588, 1365, 1208,1146,1028,875, 765 cm^{-1} m.p.: 180°C; Yield: 99.00 %; Anal. Calcd. For $C_{18}H_{17}ClN_2O_2$ (328.10): C; 65.75, H; 5.21, Cl;10.78;N,8.52%; O, 9.73%. Found C; 65.75, H; 5.21, Cl;10.78;N,8.52%; O, 9.73%.

Synthesis of 2-Amino-4-(furan-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (6).

FTIR (ATR): 3314, 2960, 2878, 2300, 1661, 1589, 1497, 1363, 1248, 1121, 1022, 971, 926 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.06 (s, 3H), 1.12 (s, 3H), 1.82 (s, 1H), 2.29 (s, 2H), 4.17 (s, 1H), 6.25 (d, 1H), 6.40 (t, 1H), 6.82 (s, 2H), 7.57 (d, 1H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=27.5, 38.9, 50.9, 51.5, 58.1, 106.7,110.6, 113.9, 114.7, 119.1, 120.3,127.7, 130.4, 144.1, 159.2, 198.9. MS (m/z): 328.10 (100.0%), 330.09(32.0%), 329.10 (19.5%),331.10 (6.02%), 330.10 (1.8%) m.p.: 221°C; Yield: 97.52 %; Anal. Calcd. For $C_{16}H_{16}N_2O_3$ (284.32): C; 67.59, H; 5.67,N;9.85%; O, 16.88%. Found C; 67.59, H; 5.67,N;9.85%; O, 16.88%.

Synthesis of 2-Amino-4-(4-hydroxy-3-methoxyphenyl)-7,7-dimethyl-5-oxo-4-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (7).

FTIR (ATR): 3742, 3668, 3609, 3498, 3393, 3313, 3195, 2966, 2880, 2303, 2187, 1652, 1584, 1510, 1449, 1364, 1252, 1148, 1034 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.06 (s, 3H), 1.12 (s, 3H), 1.82 (s, 1H), 2.29 (s, 2H), 3.77 (s,3H), 4.17 (s, 1H), 6.63 (d, 1H), 6.66 (d, 1H), 6.78 (s, 1H), 9.96 (s, 1H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=27.5,32.3, 38.9,39.7, 51.5, 56.1, 58.1,114.5,115.5, 119.1, 122.7,127.7, 130.4, 144.1, 155.0, 159.2, 198.9. MS (m/z): 340.14 (100.0%), 341.15(20.5%), 342.15 (2.0%). m.p.: 200°C; Yield: 90.41 %; Anal. Calcd. For $C_{19}H_{20}N_2O_2$ (340.14): C; 67.05, H; 5.92, N;8.23%; O, 18.80%. Found C; 67.05, H; 5.92, N;8.23%; O, 18.80%.

Synthesis of 2-Amino-4-(2-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (8).

FTIR(ATR): 3725, 2956, 2306, 1592,1453, 1373, 1231,1141,1028,0962,749 cm^{-1} ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.06 (s, 3H), 1.12 (s, 3H), 1.82 (s, 2H), 2.29 (s, 2H), 4.29 (s, 1H), 6.80 (d, 1H), 6.82 (s, 2H), 6.86 (d, 1H), 7.11 (t, 1H),7.27(d, 1H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=27.5, 31.1,32.3,38.9,39.7, 51.5, 56.1, 58.1,114.5,115.5, 119.1, 122.7,115.8, 121.2, 122.6, 127.7, 155.0, 156.1, 159.2, 198.9. MS (m/z): 310.13 (100.0%), 311.14(19.5%), 312.14 (1.8%). m.p.: 130°C; Yield: 77.72 %; Anal. Calcd. For $C_{18}H_{18}N_2O_3$ (310.35): C; 69.66, H; 5.85, N;9.03%; O, 15.47%. Found C; 69.66, H; 5.85, N;9.03%; O, 15.47%.

Synthesis of 2-Amino-4-(4-(dimethylamino)Phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (9).

FTIR (ATR): 3500, 2969, 2892, 2796, 2194, 1661, 1592, 1518, 1362, 1233, 1156, 1062, 927, 810, 719 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.06 (s, 3H), 1.12 (s, 3H), 1.82 (s, 2H), 2.29 (s, 2H), 3.02(s, 6H), 4.29 (s, 1H), 6.56 (d, 2H), 6.82 (s, 2H), 6.95 (d, 2H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=27.5, 31.1, 32.3, 38.9,39.7, 41.3, 58.1,112.0, 113.9, ,115.8, 119.1 121.2, 122.6, 127.7, 128.1, 156.1, 159.2, 198.9. MS (m/z): 337.18 (100.0%), 338.18(21.6%), 339.19 (2.2%). m.p.: 160°C; Yield: 72.91 %; Anal. Calcd. For $C_{20}H_{23}N_3O_2$ (337.18): C; 71.19, H; 6.87, N;12.45%; O, 9.48%. Found C; 71.19, H; 6.87, N;12.45%; O, 9.48%.

Synthesis of 2-Amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (10).

FTIR (ATR): 3400, 2973, 2897, 2186, 1670,1542, 1414, 1342,1231,1182,989, 859 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d6) δ ppm): δ=1.06 (s, 3H), 1.12 (s, 3H), 1.82 (s, 2H), 2.29 (s, 2H), 4.29 (s, 1H), 6.61 (d, 2H),6.82(s,2H), 6.98 (s, 2H), 9.06(s, 1H). ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ=27.5, 31.1,32.3,38.9,39.7, 51.5, 56.1, 58.1,114.5,115.5, 119.1, 122.6, 130.4, 155.5, 156.1, 159.2, 198.9. MS (m/z): 310.13 (100.0%), 311.14(19.5%), 312.14 (1.8%). m.p.: 206°C; Yield: 82.00 %; Anal. Calcd. For $C_{18}H_{18}N_2O_3$ (310.13): C, 69.66; H, 5.85; N, 9.03, O, 15.47%. Found C, 69.66; H, 5.85; N, 9.03, O, 15.47%.

RESULT AND DISCUSSION

Comparison of solvents

2-Amino-4-aryl-4H-chromene and its derivatives synthesized using Dimedone, Malononitrile and different aldehyde in 1:1:1 stoichiometric ratio. Morpholine is used 5mmol as a green catalyst and water used as a green solvent. 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 Dimedone 1, malononitrile 2, and 3- chloro benzaldehyde to afford 2-Amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e)

No.	Solvent	Time (min)	Yield %
1	No solvent	05	Trace
2	Water	02	99%
3	Ethanol	05	80%
4	Methanol	05	76%
5	n-Hexane	15	30%
6	Acetone	10	65%
7	Propanol	10	68%
8	Toluene	15	--

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 irradiation 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. 2-Amino-4-(phenyl derivatives)-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile under sonication and conventional conditions.

No.	**Compound**	**- R**	**Ultrasonic irradiation**		**Conventional method**	
			Time (min)	**Yield (%)**	**Time (minutes)**	**Yield (%)**
1	**4a**	C_6H_5	2	92.40 %	270- 360	< 90%
2	**4b**	4-Cl-C_6H_4	2	83.80 %	270- 360	< 90%
3	**4c**	3-OH-C_6H_4	2	71.82 %	270- 360	< 90%
4	**4d**	4-NO_2-C_6H_4	3	85.12 %	270- 360	< 90%
5	**4e**	3-Cl-C_6H_4	3	99.00 %	270- 360	< 90%
6	**4f**	C_4H_4O	2	97.52 %	270- 360	< 90%
7	**4g**	4-OH-3-OCH_3-C_6H_3	3	90.41 %	270- 360	< 90%
8	**4h**	3-OH-C_6H_4	3	77.72 %	270- 360	< 90%
9	**4i**	4-$(CH_3)_2$-C_6H_4	3	72.91 %	270- 360	< 90%
10	**4j**	4-OH-C_6H_4	3	82.00%	270- 360	< 90%

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

No.	**Amount of morpholine (equivalent %)**	**Time (min)**	**Yield %**
1	Trace	02	Trace
2	5	02	99
3	10	04	94
4	15	06	92
5	20	05	92
6	25	05	90
7	30	05	87

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

No.	**Solvent**	**Time (min)**	**Yield %**
1	Water	02	99
2	Water	05	97
3	Water	10	97
4	Water	15	97
5	Water	20	97
6	Water	25	97

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

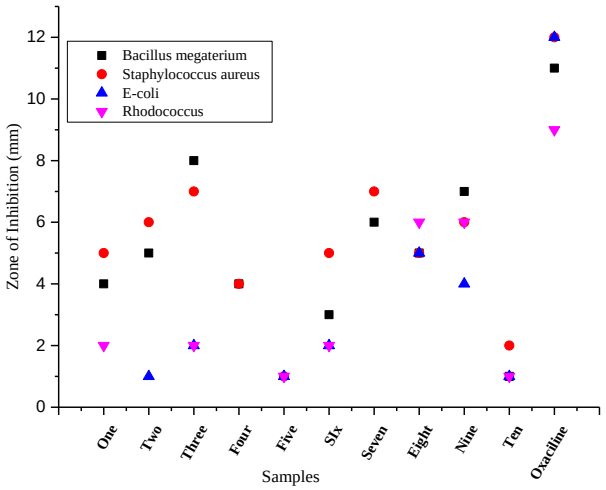
No.	**Solvent**	**Temperature (C˚)**	**Time (min)**	**Yield %**
1	Water	20	5	80
2	Water	25	5	82
3	Water	30	5	85
4	Water	35	2	99
5	Water	40	5	80
6	Water	45	5	80
7	Water	50	5	80

Antimicrobial activity

Antibacterial activities The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Bacillus megaterium, Staphylococcus aureus and Rhodococcus*) and gram-negative bacteria (*E. coli*) at a concentration of 50μg/ML by agar diffusion assay xxiii,xxiv. The wells were dug in the media with the help of a sterile metallic borer. Recommended concentration (100 μl) of the test sample (1 mg/mL in DMSO) was introduced in the respective wells. Other wells supplemented with DMSO and reference antibacterial drug Oxacilline was served as negative and positive controls, respectively. The plates were incubated immediately at 37˚C for 24 hours. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard drug Oxacilline. The percentage area of inhibition of zone measured. In order to clarify any participating role of DMSO in the biological screening, separate studies were carried out with the solutions alone of DMSO and they showed no activity against any bacterial strains. Compounds 4e were found more toxic for microbes. Other compounds found to be less or moderate active shown in Table-6.

Table 6. Antibacterial Activity of Compounds (4a-j)

			Zone Of Inhibition (Millimetre)			
Sr. No.	**SAMPLES**	**Compound**	***Bacillus megaterium***	***Staphylococcus aureus***	***Rhodococcus***	***E-coli***
1	01	**4a**	4	5	2	--
2	02	**4b**	5	6	--	1
3	03	**4c**	8	7	2	2
4	04	**4d**	4	4	--	--
5	05	**4e**	--	1	1	1
6	06	**4f**	3	5	2	2
7	07	**4g**	6	7	--	--
8	08	**4h**	5	5	6	5
9	09	**4i**	7	6	6	4
10	10	**4j**	1	2	1	1
11	Standard (Oxacillin)		11	12	9	12



CONCLUSION:

We have devised a green method for the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives by using water as a green solvent in a multicomponent, one-pot reaction that is irradiated with ultrasonic waves. This method offers many benefits, including higher product yields, a quicker response time, and simple setup. In this study, we can witness a comparison between green and conventional procedures. Lastly, the green strategy generates a rapid increase in production. This result suggested that optimization studies, which offer data on different solvents, time, temperature, and base amount, had been conducted. Ultimately, we believe that using water as a solvent in this procedure is the most effective approach to get the greatest outcomes. The antimicrobial activities of mostly the compounds were showed good activities.

ACKNOWLEDGEMENTS:

The authors would like to express their gratitude to the Pramukh Swami Science and H D Patel Arts Colleges Kadi, Mehsana, Gujarat.

REFERENCE:

i. Auria-Luna. F.; Fernández-Moreira V.; Marqués-López. E.; Gimeno M.C.; Herrera RP.; Ultrasound-assisted multicomponent synthesis of 4H-pyrans in water and DNA binding studies; Scientific reports; 2020, **10** (1), 1-17.

ii. Isambert. N.; Duque. MdMS; Plaquevent J. C.; Genisson. Y.; Rodriguez. J.; Constantieux. T.; Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis; Chemical Society Reviews.; 2011, **40** (3),1347-57.

iii. Kamalzare M.; Bayat M.; Maleki A.; Green and efficient three-component synthesis of 4H-pyran catalysed by CuFe2O4@ starch as a magnetically recyclable bionanocatalyst.; Royal Society open science.; 2020, **7** (7), 200385.

iv. Kalhor S.; Yarie M.; Rezaeivala M.; Zolfigol MA.; Novel magnetic nanoparticles with morpholine tags as multirole catalyst for synthesis of hexahydroquinolines and 2-amino-4, 6-diphenylnicotinonitriles through vinylogous anomeric-based oxidation. Research on Chemical Intermediates.; 2019, **45**(6), 3453-80.

v. Azizi S,; Soleymani J, Hasanzadeh M.; Iron oxide magnetic nanoparticles supported on amino propyl-functionalized KCC-1 as robust recyclable catalyst for one pot and green synthesis of tetrahydrodipyrazolopyridines and cytotoxicity evaluation. Applied Organometallic Chemistry.; 2020,**34**(3), e5440.

vi. Pratap UR.; Jawale DV.; Netankar PD, Mane RA. Baker's yeast catalyzed one-pot three-component synthesis of polyfunctionalized 4H-pyrans. Tetrahedron Letters.; 2011, **52**(44),5817-9.

vii. Naeimi H.; Zarabi MF.; A facile one-pot ultrasound-assisted green synthesis of tetrahydrobenzo [b] pyrans catalyzed by gold nanoparticles supported on thiol-functionalized reduced graphene oxide. Research on Chemical Intermediates.; 2018,**44**(5),3227-47.

viii. Heravi MM.; Zakeri M.; Pooremamy S.; Oskooie HA.; Clean and efficient synthesis of polyhydroquinoline derivatives under solvent-free conditions catalyzed by morpholine. Synthetic Communications®.; 2010,**41**(1),113-20.

ix. Eshtehardian B.; Rouhani M.; Mirjafary Z.; Green protocol for synthesis of MgFe2O4 nanoparticles and study of their activity as an efficient catalyst for the synthesis of chromene and pyran derivatives under ultrasound irradiation.; Journal of the Iranian Chemical Society.; 2020,**17** (2),469-81.

x. Esmaeilpour M.; Javidi J.; Dehghani F.; Dodeji FN.; A green one-pot three-component synthesis of tetrahydrobenzo [b] pyran and 3, 4-dihydropyrano [c] chromene derivatives using a Fe 3 O 4@ SiO 2–imid–PMA n magnetic nanocatalyst under ultrasonic irradiation or reflux conditions. RSC Advances.; 2015, **5**(34),26625-33.

xi. Edjlali L.; Hosseinzdeh-Khanmiri R.; γ-alumina catalyzed green synthesis of Pyran's annulated heterocyclic systems via three-component reaction. Iranian Journal of Science and Technology, Transactions A: Science.; 2016,**40**(2),151-6.

xii. Dandia A.; Gupta SL,; Parewa V.; Sharma A.; Rathore KS. "On-water" synthesis of 3-substituted indoles via Knoevenagel/Michael addition sequence catalyzed by Cu doped ZnS NPs. Tetrahedron Letters.; 2013,**54** (42), 5711-7.

xiii. Niknam K.; Piran A.; Silica-Grafted Ionic Liquids as Recyclable Catalysts for the Synthesis of 3, 4-Dihydropyrano [c] chromenes and Pyrano [2, 3-c] pyrazoles.; 2013.

xiv. Mohareb R.; Manhi F.; Abdelwahab A.; Synthesis of heterocyclic compounds derived from dimedone and their anti-tumor and tyrosine kinase inhibitions.; Acta Chimica Slovenica.; 2020,**67**(1),83-95.

xv. Kalla R.M.N.; Bae J.; Kim I.; Catalyst-free ultrasonic-promoted multicomponent synthesis of tertiary α-amino phosphonates.; New Journal of Chemistry. 2017,**41**(14),6653-60.

xvi. Youssef MSK.; Abeed AAO, El-Emary TI.; Synthesis and evaluation of chromene-based compounds containing pyrazole moiety as antimicrobial agents. Heterocyclic Communications.; 2017, **23**(1),55-64.

xvii. Vazirimehr S.; Davoodnia A.; Nakhaei-Moghaddam M.; Tavakoli-Hoseini N.; Ultrasonic synthesis, characterization, and antibacterial evaluation of novel heterocycles containing hexahydroquinoline and pyrrole moieties. Heterocyclic Communications.; 2017,**23**(1),65-70.

xviii. Banitaba SH.; Safari J.; Khalili SD.; Ultrasound promoted one-pot synthesis of 2-amino-4, 8-dihydropyrano [3, 2-b] pyran-3-carbonitrile scaffolds in aqueous media: A complementary 'green chemistry'tool to organic synthesis. Ultrasonics sonochemistry. ;2013,**20**(1),401-7.

xix. Shende VS.; Saptal VB.; Bhanage BM.; Recent advances utilized in the recycling of homogeneous catalysis.; The Chemical Record.; 2019,**19**(9),2022-43.

xx. Nikoofar K.; Yielzoleh FM.; A concise study on dimedone: A versatile molecule in multi-component reactions, an outlook to the green reaction media. Journal of Saudi Chemical Society.;2018,**22**(6),715-41.

xxi. Draye M.; Chatel G.; Duwald R.; Ultrasound for drug synthesis: a green approach. Pharmaceuticals.; 2020,**13**(2),23.

xxii. Uozumi Y.; Osako T.; Synthesis of Tetrahydro-4H-chromenes Using Nano γ-Fe2O3 in H2O. Synfacts.;2013, **9**(09),1018.

xxiii. Kamoutsis C.; Fesatidou, M.; Petrou, A.; Geronikaki, A.; Poroikov, V.; Ivanov, M.; Soković, M.; Ćirić, A.; Carazo A.; Mladěnka, P.; Triazolo based-thiadiazole derivatives. synthesis, biological evaluation and molecular docking studies; Antibiotics.;2021, **10**(7), 804.

xxiv. Joshi, K.; Dhalani, J.; Bhatt, H.; Kapadiya, K.; Synthesis of some new 6-aryl-3-(4-isopropylphenyl)[1, 2, 4] triazolo [3, 4-b][1, 3, 4] thiadiazoles and its anti-microbial study; Current Chemistry Letters.; 2021, **10**(4), 479.

Received on February 16, 2023.