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Ultrasound-assisted Synthesis and Characterization of 5-Carbonitrile-Functionalized tetrahydropyrimidine Derivatives with Evaluation of Their Antimicrobial Activity

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ABSTRACT

The green synthesis approach employs ultrasound waves as an effective and environmentally friendly strategy to catalyze chemical reactions. Within this framework, carbonitrile-bearing tetrahydropyrimidine derivatives were successfully synthesized. This involved the reaction of malononitrile, urea or thiourea, and variously substituted aldehydes in the presence of morpholine as a catalyst, conducted in aqueous conditions under ultrasonic irradiation. Notably, this method resulted in elevated reaction yields and significantly reduced reaction times when compared to conventional approaches. The synthesized compounds underwent comprehensive characterization using various spectroscopic techniques, including UV-Vis, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. This innovative process aligns with the principles of green chemistry, emphasizing efficiency, sustainability, and the reduction of environmental impact in chemical synthesis.

Keywords: 4H-Chromene, Ultrasound-Assisted Synthesis, Green Synthesis, Antimicrobial Activity.

INTRODUCTION

The field of organic synthesis has seen significant advancements in recent years, with a focus on developing environmentally friendly and efficient methods to access structurally diverse compounds.[1] One such approach is the use of ultrasound-assisted synthesis, a powerful tool that offers several advantages over traditional synthetic techniques.[2] Ultrasound-assisted synthesis is characterized by its ability to accelerate chemical reactions through the application of high-frequency sound waves[3], leading to enhanced yields, reduced reaction times[4], and milder reaction conditions.[5]

Tetrahydropyrimidine derivatives[6] are a class of organic compounds that have garnered significant attention due to their diverse pharmacological

properties.[7] Their structural versatility makes them promising candidates for drug development[8], particularly in the context of antimicrobial agents.[9] The carbonitrile-bearing moiety in these compounds often enhances their biological activities, making them an attractive target for synthetic chemistry endeavors.[10]

The selection of inexpensive, safe, and non-toxic solvents is one of the key components of a green chemical process.[11] Water being ample in nature is the primary choice. Additionally, to meet the conditions mentioned earlier[12] Development of organic reactions in aqueous environments has been the subject of powerful scientific interest.[13]

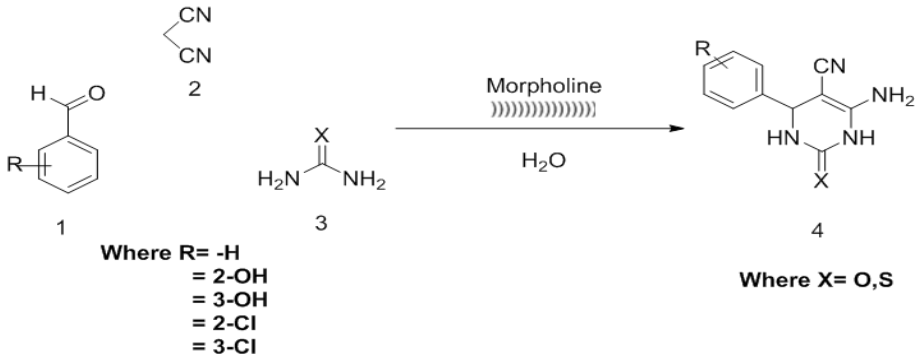
Multicomponent reactions (MCRs) have evolved as efficient chemical processes.[14] Clearly, the benefits of the current chemical reaction include a simple, rapid, efficient, and environmental friendly purification approach as well as high product yields.[15] "Today, the efficiency of a chemical synthesis may be judged not only by selectivity and total yield[16], but also by its raw material, time, human resources[17], and energy needs, as well as the toxicity and dangers of the chemicals and the procedures involved."[18]

The problematic issue of creating a modest, environmentally friendly[19], and cost-effective reaction technique for medicinal chemistry[20] is a important field of both academic and pharmaceutical research.[21] Developing MCR processes in aqueous medium is an active field of study in this direction has several benefits, including the absence of carcinogenic effects,[22] decreased pollution, lesser cost, and ease of processing, which are beneficial to both the industry and the environment.[23]

Additionally the synthesis[24] of several organic compounds with the aid of ultrasonic technology and the presence of catalysts greatly increase reaction rate[25], reduced reaction durations, decreased energy consumption[26], increased selectivity, and increased product yield. Compared to traditional procedures, these procedures have revealed to be effective, rapid, clean[27], environmentally friendly, and reliable in chemical laboratory.[28] One of the emerging areas in organic synthesis, sonochemistry, has significant promise for the development of energy-efficient[29] increase in reaction times brought on by sound waves intense effects (heterogeneous processes)[30] and chemical commencement (homogeneous processes).[31] Typically, responses encouraged by ultrasonic irradiation are modest to operate[32] than those induced by traditional means. Due to our attention in the synthesis of heterocyclic molecules[33] with possible biological activity, we were inspired by these discoveries.[34]

EXPERIMENTAL

We acquired the solvents and reagents essential for the synthesis from SDfine Chemicals and Merck Ltd company. Using the open-end capillary device, the melting points (M.P.) of the final derivatives were taken. Mobile phase consisted of a mixture of ethyl acetate:n-hexane (4:6) and TLC plates (TLC silica gel 60 F254) bought from Merck Ltd company. Using a Nicolet 400D spectrometer, the IR spectra were captured in KBr pellets. Using TMS as an internal standard, the ^{1}H and ^{13}C NMR spectra were recorded in DMSO solvent using a Bruker spectrometer functioning at 400 MHz and 100 MHz, separately. The Schmindzu mass spectrophotometer was used to determine the mass spectra data for individual derivative.



Scheme 1: Common Synthesis of tetrahydropyrimidine -5-carbonitrile

General procedure

A mixture of substituted aldehyde, malononitrile (1 mmol), and urea or thiourea (1 mmol) in water (10 mL) with catalytic amount of morpholine (0.5 mmol) was irradiated by an ultrasonic irradiation (33 kHz) at room temperature (30°C) TLC was used to monitor the reaction's completion and the mobile phase was ethyl acetate:n-hexane (4:6). The product undergoes a process involving filtration, water washing, drying, and recrystallization using ethanol. The structures of the products were analysed through the FTIR, ^{1}H NMR, ^{13}C NMR spectra and mass spectrometry.

Analytical discussion

Synthesis of 6-amino-2-oxo-4-phenyl-1, 2, 3,4-tetrahydropyrimidine-5-carbonitrile (4a) FTIR (ATR): 3500, 3300, 3020, 3100, 2950, 2850, 1750, 1650, 1350, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ =5.6 (s, 1H), 6.5 (s, 2H), 7.61 (s, 1H), 7.29-7.31 (m, 5H), 9.12 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): = 50.7, 63.4, 117.3, 126.5, 128.5, 143.5, 150.2, 158.1 MS (m/z): 214.9 (100.0%), m.p.: >200°C; Yield: 97.52%; Calculated data for $C_{11}H_{10}N_4O$ (214.29): C; 61.7, H; 4.7, N;26.2%; O, 7.4%. Found data is C; 60.67, H; 4.6 N;25.6%; O, 7.3%.

Synthesis of 6-amino-4-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4b)

FTIR (ATR): 3500, 3300, 3050, 3100, 2950, 2750, 1750, 1550, 1350, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ = 5.6 (s, 1H), 6.5 (s, 2H), 7.61 (s, 1H), 6.83-7.11 (m, 5H), 9.12 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ = 50.7, 62.4, 117.3, 125.5, 128.5, 142.5, 150.2, 157.1 MS (m/z): 230.8 (100.0%), m.p.: >200°C; Yield: 97.52%; Calculated data for $C_{11}H_{10}N_4O_2$ (230): C; 57.4, H; 4.4, N;24.34; O, 13.9%. Found data is C; 56.67, H; 4.4, N;24.6%; O, 12.4%.

Synthesis of 6-amino-4-(3-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(4c)

FTIR (ATR): 3500, 3200, 3020, 3160, 2950, 2750, 1750, 1550, 1350, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ =5.6 (s, 1H), 6.6 (s, 2H), 7.63 (s, 1H), 6.82-7.08 (m, 5H), 9.11 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ , ppm): δ = 50.7, 63.4, 117.3, 126.5, 128.5, 143.5, 150.2, 158.1 MS (m/z): 230.8 (100.0%), m.p.: >200°C; Yield: 95.52 %; Calculated data for $C_{11}H_{10}N_4O_2$ (230): C; 61.7, H; 4.7, N;26.2%; O, 7.5%. Found data is C; 60.7, H; 4.7, N;25.6%; O, 7.5%.

Synthesis of 6-amino-4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4d)

FTIR (ATR): 3400, 3250, 3020, 3150, 2950, 2760, 1750, 1500, 1350, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ = 5.4 (s, 1H), 6.50 (s, 2H), 7.61 (s, 1H), 7.21-7.68 (m, 4H), 9.12 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ = 45.6, 50.7, 63.4, 117.3, 126.5, 132.5, 143.5, 150.2, 158.2 MS (m/z): 248.05 (100.0%), m.p.: >200°C; Yield: 96.52 %; Calculated data for C11H9ClN4O (248): C; 53.2, H; 3.7, Cl; 14.3, N; 22.6%, O;6.4%. Found data is C; 50.7, H; 2.7, Cl;13.3, N;21.6%; O, 5.5%.

Synthesis of 6-amino-4-(3-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(4e)

FTIR (ATR): 3450, 3200, 3020, 3150, 2850, 2760, 1750, 1400, 1360, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ =5.4 (s, 1H), 6.51 (s, 2H), 7.61 (s, 1H), 7.15-7.46 (m, 4H) , 9.12 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ = 40.6, 50.7, 63.4, 117.3, 126.5, 131.5, 143.5, 150.2, 158.2 MS (m/z): 248.05 (100.0%), m.p.: >200°C; Yield: 96.52%; Calculated data for $C_{11}H_9ClN_4O$ (248): C; 53.1, H; 3.7, Cl;14.3, N;22.5%, O;6.4%. Found data is C; 50.7, H; 2.7, Cl;13.3, N;21.6%; O, 5.5%.

Synthesis of 6-amino-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(4f)

FTIR (ATR): 3500, 3230, 3020, 3050, 2830, 2650, 1750, 1400, 1320, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ = 5.2 (s, 1H), 6.50 (s, 2H), 7.62 (s, 1H), 6.80-7.30 (m, 5H), 9.12 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ =40.6, 50.7, 63.4, 117.3, 126.5, 131.5, 143.5, 150.2, 158.2 MS (m/z): 230.06 (100.0%), m.p.:>200°C; Yield: 92.52%; Calculated data for $C_{11}H_{10}N_4S$ (230.3): C; 57.4, H; 4.4, N;24.3%, S;13.9%. Found data is C; 56.7, H; 3.9, N;23.6%; S; 12.4%.

Synthesis of 6-amino-4-(2-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4g)

FTIR (ATR): 3500, 3230, 3020, 3050, 2830, 2650, 1750, 1400, 1320, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ =5.1 (s, 1H), 6.48 (s, 2H), 7.60 (s, 1H), 6.83-7.30 (m, 4H), 9.7 (s, 1H), 9.2 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ = 42.6, 50.7, 63.4, 117.3, 127.5, 131.5, 143.5, 150.2, 157.2 MS (m/z): 246.1 (100.0%), m.p.:>200°C;

Yield: 32.52%; Calculated data for $C_{11}H_{10}N_4OS$ (246.3): C; 57.4 , H; 4.4, N;22.7%, S;13.9%. Found data is C; 56.7, H; 3.9, S; 12.5%, N;22.6%.

Synthesis of 6-amino-4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile(4h)

FTIR (ATR): 3400, 3250, 3020, 3030, 2850, 2650, 1750, 1200, 1350, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ = 5.2 (s, 1H), 6.45 (s, 2H), 7.60 (s, 1H), 7.10-7.35 (m, 4H), 9.5 (s, 1H), 9.6 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ = 42.6, 50.7, 63.4, 117.3, 127.5, 131.5, 143.5, 150.2, 157.2 MS (m/z): 246.06 (100.0%), m.p.:>200°C; Yield: 32.5%; Calculated data for $C_{11}H_{10}N_4OS$ (246.3): C; 53.6, H; 4.1, N;23.7%, S;13.1%. Found data is C; 52.7, H; 3.9, N;22.7%; S; 12.6%.

Synthesis of 6-amino-4-(2-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4i)

FTIR (ATR): 3500, 3250, 3050, 3030, 2850, 2650, 1750, 1250, 1350, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ = 5.3 (s, 1H), 6.43 (s, 2H), 7.60 (s, 1H), 6.83-7.30 (m, 4H) , 9.7 (s, 1H), 13C NMR (100MHz, DMSO-d6, δ, ppm): δ = 42.6, 50.7, 63.4, 117.3, 127.5, 131.5, 143.5, 150.2, 157.2 MS (m/z): 246.06 (100.0%), m.p.:>200°C; Yield: 32.52%; Calculated data for $C_{11}H_9ClN_4S$ (264.7): C; 49.9, H; 3.4, Cl;13.4, N;21.1, S;12.1%. Found data is C; 48.7, H; 3.4, Cl;13.3, N;20.7%; S; 12.1%.

Synthesis of 6-amino-4-(3-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (4j)

FTIR (ATR): 3500, 3250, 3050, 3030, 2850, 2650, 1750, 1250, 1350, 1000 cm^{-1}. Spectra ^{1}HNMR (400 MHz, DMSO-d6 δ ppm): δ = 5.3 (s, 1H), 6.45 (s, 2H), 7.6 (s, 1H), 7.11-7.30 (m, 4H) , 9.7 (s, 1H), ^{13}C NMR (100MHz, DMSO-d6, δ, ppm): δ = 42.6, 50.7, 63.4, 117.3, 127.5, 131.5, 143.5, 150.2, 157.2 MS (m/z): 246.1 (100.0%), m.p.:>200°C; Yield: 32.5%; Calculated data for $C_{11}H_9ClN_4$ (264.73): C; 49.9 , H; 3.4 , Cl;13.4, N;21.1 , S;12.1%. Found data is C; 48.7, H; 3.4, Cl;13.3, N;20.7%; S; 12.1%.

RESULT AND DISCUSSION

Comparison of solvents

2-Amino-4-aryl-4H-chromene and its derivatives synthesized using urea or thiourea, malononitrile and different aldehyde in 1:1:1 stoichiometric ratio. Morpholine was used as a green catalyst and water as a green solvent. The reaction was carried out under ultrasound irradiation method.

Table 1: Comparison of solvents for the reaction of urea or thiourea, malononitrile 2, and 3-chloro benzaldehyde to afford 6-amino-4-(3-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile

No	Solvent	Time (minutes)	Yield%
1	No solvent	07	Trace
2	Water	03	99%
3	Ethanol	07	80%
4	Methanol	06	76%
5	n-Hexane	10	30%
6	Acetone	10	65%
7	Propanol	15	68%
8	Toluene	15	--

Comparison of ultrasonic irradiation and conventional methods: When the reaction was carried out using the traditional approach, it gives relatively law yield and took longer to complete, but the reaction carried out under the effect of ultrasonic irradiation gives outstanding product in a fast reaction time. Thus, ultrasonic irradiation was found to be superior over the traditional technique in terms of product yield and efficiency.

Table 2: 6-amino-4-(phenyl derivatives)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrile , 6-amino-4-(phenyl derivatives)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitrilecompare study under sonication and conventional conditions

No	Compound	- R	Ultrasonic irradiation		Conventional method	
			Time (minutes)	Yield (%)	Time (minutes)	Yield (%)
1	4a (x=o)	-H	2	92.40 %	260	80%
2	4b(x=o)	2-OH	3	82.80 %	260	75%
3	4c(x=o)	3-OH	2	71.82 %	260	65%
4	4d(x=o)	2-Cl	3	83.12 %	260	75%
5	4e(x=o)	3-Cl	3	98.00 %	260	85%
6	4f (x=s)	-H	2	96.52 %	260	80%
7	4g(x=s)	2-OH	3	90.41 %	260	75%
8	4h(x=s)	3-OH	3	76.72 %	260	70%
9	4i(x=s)	2-Cl	3	72.91 %	260	65%
10	4j(x=s)	3-Cl	3	97.00%	260	85%

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

No	Amount of morpholine (equivalent %)	Time (minutes)	Yield%
1	Trace	02	Trace
2	5	03	98
3	10	04	96
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 (minutes)	Yield %
1	Water	03	98
2	Water	05	96
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

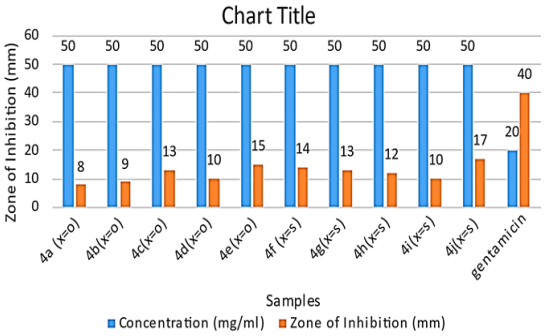
No	Solvent	Temperature(C^{o})	Time (minutes)	Yield%
1	Water	20	5	82
2	Water	25	5	82
3	Water	30	5	85
4	Water	35	3	98
5	Water	40	5	80
6	Water	45	5	80
7	Water	50	5	80

Antibacterial Activity of the given samples against *Staphylococcus aureus*

Staphylococcus aureus MTCC 7443 strain was used in the study. In Mueller Hinton, an agar well diffusion method was used to assess the mentioned microbial isolate for antibacterial susceptibility. *S. aureus* was injected into nutrient broth on agar (MHA) plates, and it was incubated at 37°C for the whole night. Bacterial culture broth was used to make culture MHA plates. Various samples in a concentration of 40–50 mg/mL were placed in dimethyl sulfoxide (DMSO). Using a sterile cork-borer as support, 6 mm wells were drilled into the inoculation medium. 50 µL of the provided samples and a positive control (gentamicin 20 mg/mL) were added to each well. It was incubate at 37°C for an entire night and to diffuse for about 30 min at room temperature. Following incubation, plates were examined to see if a clear zone had developed around the wells. A measurement of the zone of inhibition (ZOI) in millimetres was made.

Table 6: Diameter of zones of inhibition (mm) of given samples against S. aureus at 40-50 mg/mL concentration

No	Compound	-R	Concentration (mg/mL)	Zone of Inhibition (mm)
1	4a (x=o)	-H	50	8
2	4b(x=o)	2-OH	50	9
3	4c(x=o)	3-OH	50	13
4	4d(x=o)	2-Cl	50	10
5	4e(x=o)	3-Cl	50	15
6	4f (x=s)	-H	40	14
7	4g(x=s)	2-OH	50	13
8	4h(x=s)	3-OH	50	12
9	4i(x=s)	2-Cl	40	10
10	4j(x=s)	3-Cl	50	17
	S. aureus		20 (gentamicin)	40



CONCLUSION

Using water as a sustainable solvent, we have developed an ecologically friendly way to synthesise derivatives of 6-amino-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile in a one-pot multicomponent reaction under ultrasonic irradiation. This method presents several advantages, including enhanced product yields, reduced reaction times, and a straightforward setup in compare to conventional method. In this work, we observe a comparison between eco-friendly and traditional procedures. Notably, the eco-friendly approach leads to a significant boost in production efficiency. The study involves optimization studies, variations in solvents, reaction time, temperature and the quantity of the base. Ultimately, our research suggests that employing water as the solvent in this process is the most efficient means of achieving optimal results. Additionally, a noteworthy point is that many of the compounds is showing promising antimicrobial activities.

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Conflict of interest

The authors claim that they have no known financial conflicts of interest or close personal relationships that would appear to have impacted the research provided in this study.

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