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Optimization of 1,8-Naphthyridine Derivatives Using Ultrasonic Method: Synthesis, Characterization, and Enhanced Properties Study

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ABSTRACT:

The increasing concern for environmental sustainability and the need for efficient and green chemical synthesis have driven the development of alternative methods for producing new compound. Compared to more conventional techniques, ultrasonic irradiation offers improved preparation yields, a quicker reaction time and more comfortable conditions. The use of ultrasound sonication is a green and efficient synthetic method that utilizes sound waves to initiate chemical reactions. We optimized various reaction parameters, such as solvent, temperature, catalyst amount, and reaction time, to identify the best reaction conditions for the synthesis of the derivatives. Using morpholine as a catalyst in an aqueous condition and the ultrasonic irradiation method, ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate and its derivatives were synthesized by taking advantages of this. Synthesized compounds were confirmed through IR, ^{1}H NMR, ^{13}C NMR and mass spectra. This method provides us modern green platform to synthesize and optimize ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate derivatives.

KEY WORDS: Morpholine, Ultrasound irradiation, One pot multi-component reaction, Optimization, aqueous condition.

INTRODUCTION:

Human living standards have greatly improved since barbaric times, thanks to exceptional industrial advancement [1]. Disease-related deaths have been rapidly declining since the discovery and development of organic pharmaceutical compounds. However, these advancements come with their own set of consequences. We are currently facing a constant global threat of environmental pollution, and we have seen catastrophic global consequences of rapid industrialization and carbon footprints [2-3]. This crisis has prompted synthesis scientists to seek alternative solutions for synthesising and developing biologically and environmentally important compounds using significantly lower levels of chemical waste and less toxic methods [4-6]. Our research team is working to avoid and reduce hazardous metals, toxic solvents, and harmful chemicals used in the synthesis chemical process. Bio-based techniques, microwave irradiation, ultrasonic irradiation, and bio-based techniques are just a few of the numerous environmentally friendly and sustainable green synthesis methods available [7-8]. One-pot multicomponent reactions are a novel approach for creating or breaking bonds in heterocyclic compounds with high atom economy, and the reacting components can be changed to make them more diverse. The large number of organic reactions resulted in higher yields, shorter reaction times, and milder conditions. The application of ultrasonic effects to chemical processes is known as sonochemistry. Water is being used as a green solvent in a variety of procedures because it is environmentally friendly and produces good yields. Water is less expensive and easier to use, giving MCRs something to aim for [7-8]. Heterocycles containing naphthyridine have fascinating properties, making them a potential MCR target. The naphthyridine molecule is found in many nitrogen-containing heterocyclic natural substances and has long been known for its pharmacological and biological properties [9-11]. The term "naphthyridine" refers to the fused-ring system formed by the fusion of two pyridine rings via two neighbouring carbon atoms, with each ring containing only one nitrogen atom. Other names for this chemical family include diazanaphthalenes and pyridopyridines, but the term "naphthyridine" is the most commonly used. The nitrogen's positions in the bicyclic system are used to characterise six different isomeric forms of naphthyridines. Six alternative isomeric forms of naphthyridines are characterised based on the location of the nitrogens in the bicyclic system [12].

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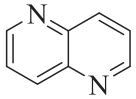
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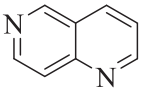
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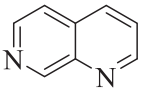
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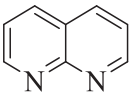
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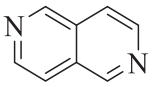
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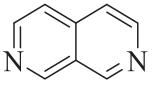
2,7-Naphthyridine
6

Scientists are interested in 1,8-naphthyridine derivatives, which are one of six isomeric sub-classes. Because of their wide range of biological activity, 1,8-naphthyridine derivatives have sparked a lot of attention. For example, the medicinal properties of 1,8-naphthyridine derivatives are promising, including antibacterial [13], anticancer [14], anti-HIV [15] and anti-parasitic activity [16].

EXPERIMENTAL:

We used commercially available solvents and reagents. TLC plates were used to perform analytical thin layer chromatography. It has a silica gel G coating to monitor reactions and determine retardation factors. TLC spots were visible inside an iodine chamber. The melting points of newly synthesised derivatives were measured using an electrothermal melting point apparatus and found to be uncorrected. The mass spectra were obtained using a SHIMADZU LC-MS 2010 spectrometer. The 13C NMR spectra were recorded on a Varian Mercury-400, 100 MHz in $CDCl_3$ with TMS as an internal standard using a 5 mm tube on a Bruker Advance II 400 MHz.

GENERAL PROCEDURE:

Ultrasound irradiation for the synthesis of ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate

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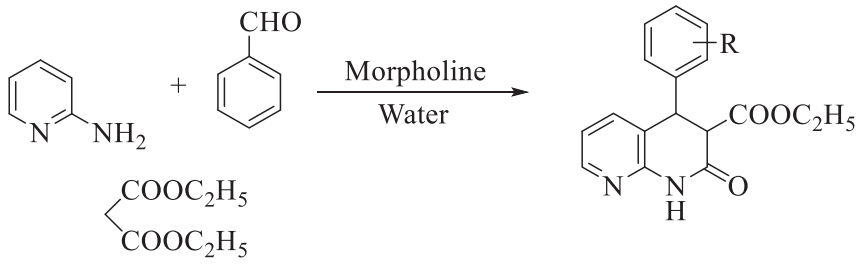
A mixture of 2-amino pyridine (9 mmol), diethyl malonate (9 mmol), and substituted aldehyde (9 mmol) in water (10 ml) with a catalytic amount of Morpholine (5 mmol) was irradiated using an ultrasonic irradiation (33 kHz) at room temperature (30˚C). TLC was used to monitor reaction completion with n-hexane and ethyl acetate (60:40 v/v) as the mobile phase. The final product was obtained after filtering, washing with water (5 mL), drying, and recrystallizing from ethanol.



Where R= -H, 4-NO_2, 4-OH, 3-OH, 2-OH, 3-Cl, 4-$N(CH_3)_2$, Furfural

ANALYTICAL DISCUSSION:

Synthesis of ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4a)

Pale yellow; Yield: (79%); mp: 80 ˚C; IR: 3310, 1660, 1257 cm^{-1}; 1H NMR(400 MHz, $CDCl_3$, δ, ppm): δ= 1.20 (t, 3H, CH_3), 4.20 (s, 1H, CH), 4.4 (s, 1H, CH), 4.6 (q, 2H, CH_2), 6.87-8.40 (m, 3H, ArH), 7.18-7.22 (m, 5H, ArH), 10.26 (s, 1H, NH); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): δ= 14.2, 43.7, 59.0, 60.9, 118.0, 125.9, 127.7, 128.6, 130.3, 137.0, 140.2, 144.0, 144.2, 169.9, 172.7. MS (m/z): 297.0 M+.

Synthesis of ethyl 4-(4-nitophenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4b)

Brown; Yield (82%); mp: 100˚C; IR: 3220, 2210, 1660, 1257 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$, δ, ppm): δ= 1.25 (t, 3H, CH_3), 4.0 (d, 1H, CH), 4.30 (q, 2H, CH_2), 4.90 (d, 1H, CH), 6.88-7.73 (m, 3H, ArH), 7.45-8.16 (m, 4H, ArH), 11.00 (s, 1H, NH); 13C NMR (100 MHz,

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$CDCl_3$, δ, ppm): δ= 15.0, 44.8, 60.3, 62.4, 119.2, 124.6, 127.5, 130.6, 138.1, 144.3, 144.6, 146.3, 148.0, 165.2, 175.0. MS (m/z): 342.0 M+.

Synthesis of ethyl 4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4c)

Orange; Yield (90%); mp: 110 ˚C; IR: 3308, 3200, 1670, 1255 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$, δ, ppm): δ = 1.33 (t, 3H, CH_3), 4.0 (d, 1H, CH), 4.35 (q, 2H, CH_2), 5.00 (d, 1H, CH), 6.77-7.23 (m, 4H, ArH), 6.89- 8.52 (m, 3H, ArH), 10.23 (s, 1H, OH) 11.29 (s, 1H, NH); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): δ = 14.1, 44.0, 60.0, 62.3, 113.5,113.9, 118.5, 120.8, 126.8, 130.5, 130.9, 137.2, 144.3, 144.7, 168.2, 172.3. MS (m/z): 313.0 M+.

Synthesis of ethyl 4-(3-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4d)

Orange; Yield (80%); mp: 110 ˚C; IR: 3308, 3200, 1670, 1255 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$, δ, ppm): δ = 1.33 (t, 3H, CH_3), 4.0 (d, 1H, CH), 4.35 (q, 2H, CH_2), 5.00 (d, 1H, CH), 6.77-7.23 (m, 4H, ArH), 6.89- 8.52 (m, 3H, ArH), 10.23 (s, 1H, OH) 11.29 (s, 1H, NH); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): δ = 14.1, 44.0, 60.0, 62.3, 113.5,113.9, 118.5, 120.8, 126.8, 130.5, 130.9, 137.2, 144.3, 144.7, 168.2, 172.3. MS (m/z): 313.0 M+.

Synthesis of ethyl 4-(2-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4e)

Orange; Yield (77%); mp: 1105 ˚C; IR: 3310, 3205, 1675, 1247 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$, δ, ppm): δ = 1.30 (t, 3H, CH_3), 4.25 (d, 1H, CH), 4.87 (q, 2H, CH_2), 5.00 (d, 1H, CH), 6.72-7.20 (m, 4H, ArH), 6.94- 8.29 (m, 3H, ArH), 10.20 (s, 1H, OH) 11.28 (s,1H, NH); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): δ = 14.1, 44.0, 60.0, 62.3, 113.5,113.9, 118.5, 120.8, 126.8, 130.5, 130.9, 137.2, 144.3, 144.7, 168.2, 172.3. MS (m/z): 313.0 M+.

Synthesis of ethyl 4(3-chlorophenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4f)

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Light yellow; Yield (75%); mp 98 ˚C; IR: 3111, 2208, 1645, 1275 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$, δ, ppm): δ = 1.22 (t, 3H, CH_3), 4.00 (d, 1H, CH), 4.50 (q, 2H, CH_2), 5.02 (d, 1H, CH), 6.88-8.45 (m, 3H, ArH), 7.00-7.30 (m, 4H, ArH); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): δ = 15.2, 45.2, 60.3, 62.1, 118.4, 125.4, 126.8, 127.6, 130.5, 131.4, 135.1, 137.8, 142.3, 145.7, 146.2, 167.5, 173.3. MS (m/z): 331.0 M+.

Synthesis of ethyl 4(4-(dimethylamino) phenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4g)

Yellow; Yield (70%); mp: 102 ˚C; IR: 3300, 1656, 1247 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$, δ, ppm): δ = 1.23 (t, 3H, CH_3), 3.00 (s, 6H, CH_3), 3.87 (d, 1H, CH), 4.25 (q, 2H, CH), 5.21 (d, 1H, CH), 6.88- 8.12 (m, 3H, ArH), 6.62-7.12 (m, 4H, ArH); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): δ = 18.2, 45.3, 48.1, 62.8, 65.1, 112.4, 118.2, 127.3, 129.4, 132.2, 137.0, 144.2, 146.8, 148.2, 170.3, 173.6. MS (m/z): 340.0 M+.

Synthesis of ethyl 4-(furan-2-yl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4h)

Brown; Yield (72%); mp: 120 ˚C; IR: 3210, 1660, 1250 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.24 (t, 3H, CH_3), 4.00 (d, 1H, CH), 4.29 (q, 2H, CH_2), 5.22 (d, 1H, CH), 6.12-7.45 (m, 3H, ArH), 6.84-8.70 (m, 3H, ArH), 11.23 (s, 1H, NH); 13C NMR (100 MHz, $CDCl_3$, δ, ppm): δ = 14.1, 36.2, 57.3, 60.8, 105.8, 110.0, 118.2, 130.2, 137.8, 141.7, 144.6, 146.2, 157.4, 168.1, 173.7. MS (m/z): 287.0 M+.

RESULT AND DISCUSSION:

Comparison of solvents

Ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate and its derivatives were synthesized in a 1:1:1 stoichiometric ratio with 2-amino pyridine, diethyl malonate and various substituted aldehydes. Morpholine (5 mmol) is used as a catalyst, while water serves as a green solvent. The reaction occurs as a result of the ultrasonic irradiation approach. A

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reaction was designed as a model to find out the optimum solvent, which is illustrated in Table No. 1.

Table 1: The use of different solvents for the reaction of 2-amino pyridine 1, diethyl malonate 2 and 4-hydroxybenzaldehyde 3 to afford ethyl 4-(4-hydroxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (4c)

No.	Solvent	Time (min)	Yield (%)
1	Solvent free	08	None
2	Water	04	90
3	Ethanol	06	82
4	Methanol	06	74
5	Acetone	10	64
6	n-Hexane	17	-
7	Toluene	18	-

Comparison of ultrasonic irradiation and conventional methods:

Ultrasound irradiation is a type of irradiation that employs enhanced sound to determine how ultrasound affects a specific reaction. When the reaction was carried out traditionally, it produced low product yields and took longer to complete; however, when carried out with ultrasonic irradiation, it produced excellent product yields in a short reaction time. Ultrasonic irradiation provided better results than the traditional method in terms of yield, reagents and yield of ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carbonitrile derivatives.

Table 2: Synthesis of ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carbonitrile derivatives in both ultrasonic irradiation and conventional method.

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No.	Compounds	-R	Ultrasonic irradiation		Conventional irradiation	
			Time (min)	Yield (%)	Time (min)	Yield (%)
1	4a	-H	08	79	120	50
2	4b	4-NO_2	08	82	90	41
3	4c	4-OH	04	90	100	45
4	4d	3-OH	07	80	120	54
5	4e	2-OH	06	77	110	50
6	4f	3-Cl	07	75	120	45
8	4g	4-$N(CH_3)_2$	08	70	180	50
9	4h	Furfural	06	72	90	40

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

No.	Amount of Morpholine	Time (min)	% Yield of 4c
1	Trace	10	Trace
2	5	04	90
3	10	06	83
4	15	08	76
5	20	10	70

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6	25	14	64
7	30	20	58

Table 4: Effect of the reaction time on the yield of 4c in water under ultrasonication

Entry No.	Time, min	% Yield of 4c
1	04	90
2	08	81
3	15	76
4	20	68
5	27	60

Table 5: Effect of temperature on the yield of 4c in water under ultrasonication

Entry No.	Solvent	Temperature, °C	Time, min	Yield of %
1	Water	30	04	90
2	Water	40	07	80
3	Water	50	12	74
4	Water	60	18	62

CONCLUSION:

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The synthesis of ethyl 2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine-3-carbonitrile derivatives was done in a one-pot multicomponent reaction under ultrasonic irradiation using water as a green solvent. Higher product yields, quicker reaction times and simplicity of setup are just a few benefits of this method. This study compares traditional and green methods. Ultimately, the green approach produces a larger yield quickly. This result showed the success of optimisation studies, which yield information on range of solvents, time, temperature and base quality among other things. In conclusion, we find that the best results are obtained when the solvent in this method is water.

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