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ENHANCING REACTION EFFICIENCY IN THE GREEN PREPARATION OF 2-(2-OXOINDOLIN-3-YLIDENE)MALONONITRILES WITH ULTRASOUND-ASSISTED KNOEVENAGEL CONDENSATION

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ABSTRACT

The development of 2-(2-oxoindolin-3-ylidene)malononitrile analogs has been quantitatively reported using an exceedingly feasible green methodology. This protocol involves the Knoevenagel condensation of various isatins and indeno[1,2-b]quinoxalin-11-nones with malononitrile in a solvent of EtOH under ultrasonic irradiation. This method significantly enhances the reaction efficiency, offering enormous yields ranging from 80% to 96% for the target products within a remarkably short reaction time of 10 to 15 minutes at ambient temperature. The synthesized 2-(2-oxoindolin-3-ylidene)malononitrile analogs were meticulously validated using NMR and FTIR spectroscopic analysis, confirming their structures. The methodology employed not only achieves exceptional yields but also features several green chemistry advantages, including simple workup procedures, the absence of column chromatography, the use of eco-friendly solvent, high tolerance for functional groups, and rapid reaction times at ambient temperature. This ultrasound-assisted approach underscores the importance of sustainable practices in chemical synthesis by minimizing energy consumption and reducing the use of hazardous reagents. The findings highlight the potential of this green protocol to be widely applicable in the development of various 2-(2-oxoindolin-3-ylidene)malononitrile analog promoting both efficiency and environmental sustainability in organic chemistry.

Keywords: Green Chemistry, 2-(2-Oxoindolin-3-Ylidene)Malononitrile, Knoevenagel Condensation, Rapid Reaction, Ultrasonic Irradiation.

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INTRODUCTION

The Knoevenagel condensation is a pivotal process in organic synthesis, renowned for its efficacy in creating novel carbon-carbon (C-C) bonds. This reaction is commonly employed for the synthesis of crucial intermediary compounds.[1] Multiple investigations have recorded the Knoevenagel condensation of isatins and indeno[1,2-b]quinoxalin-11-nones with malononitrile.[2] Two Nevertheless, conventional approaches frequently necessitate the use of perilous and variable organic bases, alkali metal hydroxides, extended reaction durations, production of byproducts, severe reaction circumstances, and laborious purification processes. To overcome these limitations, there is a significant demand for developing a novel, rapid, and environmentally friendly Knoevenagel condensation protocol that is catalyst-free. Heterocyclic compounds, which form the backbone of organic chemistry, are of particular interest due to their diverse biological activities, including antibacterial[3], antineurodegenerative[4], anticancer[5], antihyperglycemic, and antidyslipidemic properties.[6] These compounds are also found in a variety of naturally occurring substances.[7] Consequently, there is substantial scientific interest in synthesizing heterocyclic molecules through more sustainable and eco-friendly methods. In recent years, ultrasound (US) irradiation has emerged as a prominent technique within the field of green chemistry, attracting attention from both researchers and industry professionals.[8] The application of US irradiation in organic

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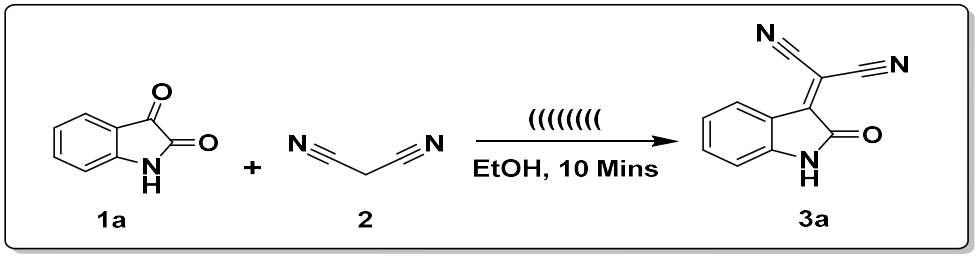
transformations has been shown to enhance yields, reduce reaction times, and facilitate reactions under milder conditions.[9] Compared to conventional methods, US-mediated reactions offer significant advantages, particularly in the development of heteroaromatic compounds.[10] The high pressures and temperatures generated within cavitation bubbles during US irradiation, along with improved mass transfer in the liquid phase, significantly influence chemical reactivity.[11-12] US irradiation boasts several environmentally friendly attributes, including short reaction times, enhanced rate of reactions, non-hazardous circumstances, high yields, gentle reaction conditions, and ease of handling.[13] Given the significance of ultrasound irradiation in the development of heterocyclic compounds, recent advancements in this field have been extensively reviewed, highlighting progress from 2009 to the present.[14] Our research group has contributed to this area, focusing on the ultrasound-mediated green synthesis of heterocyclic compounds, aiming to develop more efficient and sustainable synthetic methods.[15] To the best of my awareness, we are displaced to here the first report, utilizing the ultrasonic-mediated green synthesis of 2-(2-oxoindolin-3- ylidene) malononitrile analogues. Summary of previous tactics for the synthesis of 2(2-oxoindolin-3-ylidene) malononitrile analogues using various methods including drawbacks of the approaches viz. utlization of nano-material[15], temperature[16] and access of only few derivatives[17-18] which their comparison with present report ultrasonic mediated green-synthesis of biological active heterocyclic compounds are shown in Scheme-1. In this study, we present an environmentally benign and efficient protocol for the development of 2-(2-oxoindolin-3-ylidene)malononitrile analogues. This method employs the Knoevenagel condensation between isatins and indeno[1,2-b]quinoxalin-11-nones with malononitrile in EtOH as a solvent under ultrasound irradiation. The protocol offers significant advantages such as high yields, rapid reaction times, and the use of a green solvent, making it an attractive alternative to conventional synthetic methods. The synthesized compounds were characterized using NMR and FTIR spectroscopy, affirming the robustness and effectiveness of this green synthetic approach.



Scheme-1: Reaction Preparation of 2-(2-oxoindolin-3-ylidene)malononitrile

EXPERIMENTAL

Material and Methods

All chemicals and solvents were obtained from Sigma Aldrich and Alpha Aesar Company and utilized as received without additional purification. The 1H NMR spectra were obtained using Avance 500 spectrometers, with deuterated chloroform ($CDCl_3$) as the solvent. Chemical shifts (δ) are expressed in parts per million (ppm) with respect to residual chloroform ($CHCl_3$) (1H: δ 7.26 ppm) as an internal reference. The values of coupling constants (J) are often expressed in units of Hertz (Hz). The indication of peak multiplicity is as follows: s—representing a singlet, d—representing a doublet, t—representing a triplet, q—representing a quartet, m—representing a multiplet, and dd—representing a double doublet. The Thermo Nicolet FT/IR-5700 spectrometer was used to record the IR spectra. The mass spectra were obtained using a Waters mass spectrometer. The reactions are conducted using the Spectra-lab model UMC-20 Ultrasonic-cleaner, which operates at a frequency of 40 kHz and has a nominal power of 250 W. The melting points of the target molecules were measured using an Electrothermal (type 9100) machine and were not adjusted for any corrections.

General Method for Preparation of 2-(2-oxoindolin-3-ylidene) Malononitrile (3a)

The experiment consisted of loading 2 mmol of isatins/indeno[1,2-b]quinoxalin-11-nones, together with 6 mmol of malononitrile in 5 mL of ethanol, into a 25 mL round-bottom flask. The flask was then placed in

an ultrasonic irradiation bath operating at a power frequency of 100 W for duration of 10 minutes at the ambient temperature. The TLC technique was employed to observe the advancement of the reaction (with a ratio of 7.2:2.8; n-Hexane:EtOAc). The reaction temperature was determined by monitoring the fluctuation (increase or decrease) in the water level in the US chamber. Following the completion of the reaction, attenuate the reaction mixture by incorporating crushed ice. After duration of 10 minutes, the reaction mixture was condensed under vacuum, resulting in the formation of a solid. This solid was then dissolved in 20 mL of ethyl acetate (EtOAc) and subjected to centrifugation at a speed of 8000 revolutions per minute for duration of 1 hour. The filtrate is concentrated under vacuum, and the crude product is subjected to three washes with 3 mL of cold methanol each time. This process yields a chemical that is analytically pure. The compounds were described using infrared spectroscopy (IR) data. Additionally, nuclear magnetic resonance (NMR) was performed on a subset of compounds (3a, 3d, and 3g). The melting points of the compounds were compared to those reported in the literature.

RESULTS AND DISCUSSION

Scope and Optimization of the Reaction

An evaluation was conducted to determine the optimal conditions for synthesizing a 2-(2-oxoindolin-3-ylidene) malononitrile analogue. The trial reaction involved using isatins/indeno[1,2-b]quinoxalin-11-nones and malononitrile. The reaction was initially investigated in the absence and presence of several solvents (non-polar, polar protic, and aprotic) using both conventional and ultrasonic (US) irradiation. Table-1 indicates that in both solvent-free conditions and extended conventional heating in quiet, the process did not occur. When the reaction was seen in various solvent systems (Table-1, entries 3-5), non-polar solvents including Toluene, Hexane, and 1,4-Dioxane did not promote the reaction using both conventional and ultrasonic (US) conditions. Subsequently, when the reaction was consistently conducted at ambient temperature in the presence of aprotic polar solvents such as DMSO, MeCN, DMF, and THF, there was negligible evidence of reaction advancement (Table-1, entries 6-9). Nevertheless, when polar aprotic solvents were present, the reaction resulted in low product yields and shorter reaction durations, demonstrating the superiority of ultrasonic irradiation (Table-1, entries 6-9). Conventional methods of conducting the reaction were not successful even when polar protic solvents were utilized. However, when the reaction was carried out using polar protic solvents like isopropanol and EtOH in the US irradiation strategy, the reaction proceeded and produced high to outstanding yields (Table-1, entries 10-11). It is noteworthy that among the protic polar solvents, EtOH is the most effective and preferred solvent system for producing indoles. It results in significantly higher yields and requires a shorter reaction time of 10 minutes compared to isopropanol, which takes 1.5 hours and yields slightly lower results. The impact of the catalyst on the desired product and the decrease in reaction time was also investigated. The model process was studied using various organic or inorganic catalysts, including Na2CO3, TEA, NaOH, and NaHCO3, in EtOH solvent under both conventional and US irradiation conditions. The results showed moderate yields (Table-1, entries 12-15). The single-step reaction described earlier is most effective when isatins/indeno[1,2-b]quinoxalin-11-nones and malononitrile are exposed to US irradiation in an EtOH solvent under catalyst-free conditions. This reaction yields 2-(2-oxoindolin-3-ylidene)malononitrile analogues in high quantities, eliminating the need for other artificial chemical solvents and a catalyst.

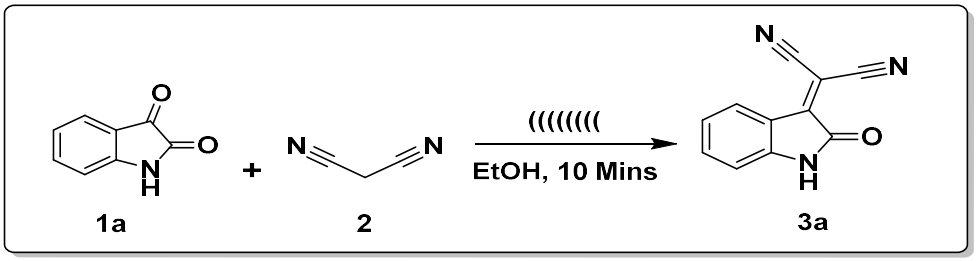
Optimization of Ultrasonic Irradiation Power

After identifying the most suitable solvent, we examined the negative impact of ultrasonic irradiation power frequency on the reaction model to discover further ideal parameters (Table-2). The device was employed at different levels of irradiation intensity in US, ranging from 25 W to 150 W. Despite the absence of US irradiation, the reaction remained incomplete even after 1 hour at ambient temperature. The growth of US influence was accompanied by consistently high model reaction product yields, leading to reduced reaction times. An impressive target yield of 96% was obtained after a mere 10 minutes after setting the US power to 100 W.

Subsequently, a diverse selection of modified isatins/indeno[1,2-b]quinoxalin-11-nones, which included both electron-withdrawing and electron-donating groups, were chosen to synthesize different 2-(2-oxoindolin-3-ylidene) malononitriles. This was done to evaluate the effectiveness of the procedure and to

refine the reaction conditions in a discreet manner. Electron withdrawing and/or electron donating groups located at the ortho, para, and meta positions of isatins/indeno[1,2-b]quinoxalin-11-nones were consistently efficient in producing the desired compounds with high yields (Table-3).

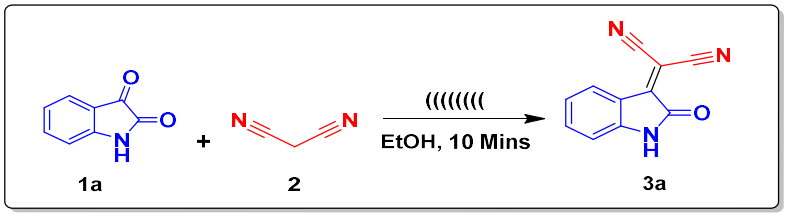
Table-1: Optimised Reaction Conditions for Preparation of 2-(2-oxoindolin-3-ylidene) Malononitrile via Knoevenagel Condensation with US and without US Conditions



Entry	Solvent	Catalyst	Temperature	Conventional		Sonication	
				Time(h)	Yield(%)	Time (h)	Yield (%)
1	No solvent	--	RM	12	--	5	--
2	No solvent	--	Heat	12	--	5	--
3	Toluene	--	RM	12	--	5	--
4	Hexane	-	RM	12	--	5	--
5	1,4-Dioxane	--	RM	10	--	4	10
6	DMSO	--	RM	10	--	2.3	28
7	MeCN	--	RM	8	--	2.0	40
8	DMF	--	RM	10	--	2.0	56
9	THF	--	RM	9	--	3.2	30
10	Isopropanol	--	RM	10	--	1.2	70
11	Ethanol	--	RM	10	--	0.10	96
12	Ethanol	Na_2CO_3	RM	5	52	1.10	68
13	Ethanol	TEA	RM	5	39	1.20	69
14	Ethanol	NaOH	RM	6	49	1.30	60
15	Ethanol	$NaHCo_3$	RM	5	35	1.45	45

No reaction/yield; RM: Room Temperature

Table-2: Optimized US Irradiation Power for Preparation of 2-(2-oxoindolin-3-ylidene) Malononitrile via Knoevenagel Condensation



Power (W)	Time (min)	Yield (%)
0	60	--
25	20	65
50	15	78
75	20	90
100	10	96
125	10	96
150	10	96

-- No reaction

By increasing the US irradiation power to 100 W, the findings validate that the most effective ultrasonic power for the efficient synthesis of 2-(2-oxoindolin-3-ylidene) malononitrile from isatins/indeno[1,2-

b]quinoxalin-11-nones and malononitrile in EtOH solvent under catalyst-free conditions is 100 W. The primary reason for the positive correlation between irradiation power and reaction enhancement is the augmentation in the quantity and dimensions of active cavitation bubbles. This leads to a higher collapse temperature, which in turn accelerates the reaction.

Table-3: Knoevenagel Condensation of 2-(2-oxoindolin-3-ylidene)malononitriles and 2-(11H-indeno[1,2-b]quinoxalin-11-ylidene)malononitrile Analogues

Entry[a]	R	R_1	R_2	Product*	% of Yield
1	-H	-H	-	3a	96%
2	$-CH_3$	-H	-	3b	91%
3	-Cl	-H	-	3c	92%
4	-Br	-H	-	3d	90%
5	-I	-H	-	3e	88%
6	-H	$-CH_3$	-	3f	82%
7	-H	$-CH_2$-Ph	-	3g	80%
8	-	-	-H	4a	96%
9	-	-	$-CH_3$	4b	90%
10	-	-	$-NO_2$	4c	85%

*All products are obtained within 10 minutes

Ultrasonication refers to the occurrence of chemical reactions in a liquid media under the influence of pressure waves. The heightened reaction of interest in ultrasonication is based on the detection of two components: chemical and mechanical qualities, which can be observed when ultrasonic waves scatter in an Ethanol medium. Ultrasound induces the collapse of bubbles, leading to the production of highly reactive substances and the creation of localized regions with temporarily elevated temperatures and pressures in homogeneous fluids. Sonication can enhance the agitation of materials in some instances, resulting in improved efficiency. Each of these elements possesses the capacity to expedite the reaction.

CONCLUSION

A novel and efficient approach for synthesizing 2-(2-oxoindolin-3-ylidene)malononitrile analogues at room temperature has been developed. This process involves the one-step condensation of substituted isatins/indeno[1,2-b]quinoxalin-11-nones and malononitrile in an ethanol solvent, with the assistance of ultrasonic irradiation. The technology has numerous benefits, such as simple setup, low temperatures, quick reaction times (10 minutes), safety, the utilization of environmentally friendly solvents, the avoidance of hazardous chemicals, and high product yields.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID IDs, given below:

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