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Microwave Irradiation Assisted Rapid Synthesis of Pyrimidine Derivative

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Abstract: *We have demonstrated Microwave assisted convenient and efficient method for the exclusive synthesis of functionalized pyrimidine Derivative framework under metal-free condition. This functionalized β-keto amide used to afford new diversely functionalized pyrimidine Derivative structural framework. This method is a straightforward route for the for the regioselective and Chemo selective addition of β-keto amides on aldehyde followed by reaction with thiourea to afford functionalized pyrimidine Derivative. Moreover, the method affords the high yields of the desired product under mild reaction condition from readily available starting materials. Additionally, this method is applicable for a variety of functionalized aldehyde as well as β-keto amides and thiourea. The obtained diversely functionalized β-keto amides framework is amenable for further structural manipulations, hence can be useful for the synthesis of natural products and a library of new pharmaceutically important molecules*

Keywords*:* Isatin, β-keto amides, Microwave Irradiation, pyrimidine, green synthesis

I. INTRODUCTION

The use of microwave radiation to speed up chemical reactions is known as microwave chemistry.[1] Conventional organic synthesis techniques have many drawbacks, such as the overuse of costly raw materials, lengthy processing times, and—above all—large amounts of chemical waste that add to the bioburden.[2] Chemical reactions have been carried out for centuries using traditional heating methods such as oil baths, Bunsen burners, and hot mantles. These techniques are not only time-consuming and labor-intensive, but they also waste energy and resources. [3] They also produce hot surfaces on reaction vessels, which causes reagents to break down over time and produce hazardous byproducts. These techniques' reliance on solvents [4] makes things even more difficult because many of them are harmful to the environment and human health, requiring extra recovery procedures. The limitations of traditional heating techniques can be addressed through alternative methods, with microwave technology being a prominent example.[5] For synthetic chemists, finding new synthetic pathways for compound synthesis is still a major and difficult goal. Finding the best synthetic route—one that minimizes environmental impact and lowers synthesis costs—presents significant intellectual and scientific challenges and necessitates careful strategic planning, whether through large-scale or small-scale efforts. As a result, numerous strategies are being investigated at the moment to advance green chemistry in research projects[6]. By speeding up chemical reactions, increasing yields, decreasing by products, and creating purer desired products in a cleaner way, the microwave-assisted organic synthesis approach has proven to be an effective way to increase chemical reaction efficiency.

In contrast to conventional methods that use conduction to heat the mixture, microwave heating targets the reaction mixture specifically without heating the appliance's entire surface, which is one of the method's many advantages. By reducing the production of unwanted by products, this method increases yield and guarantees a more effective synthesis process. It also avoids the requirement for significant amounts of hazardous organic solvents, which is a drawback frequently seen in conventional synthesis techniques. Microwave assisted synthesis is a shining example of green chemistry because of these features. "Environmentally benign chemistry," or "green chemistry," is a new field of study that focuses on the four R's: reuse, reduce, recycle, and recover. The main goal of green chemistry is to reduce the use

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of hazardous materials in chemical synthesis and to do away with toxic solvents. It represents a philosophy in chemical research and engineering that promotes the design of products and processes aimed at reducing the use and generation of hazardous substances, and is frequently referred to as sustainable [7]. In order to avoid producing hazardous waste, green chemistry depends on the use of eco-friendly materials.[8] Horvath et al. defined sustainable chemistry as the idea that waste production should not surpass the rate at which it can be controlled and that resources, including energy, should be used at a rate that permits natural replenishment [9].Paul Anastas and John C. Warner proposed the twelve principles of green chemistry in the 1990s [10], which promote ecologically conscious methods from the product's original design to its synthesis, processing, analysis, and final disposal.[11]

Chalcones can be converted into a variety of compounds, including pyrimidines. Heterocyclic compounds with nitrogen atoms are generally known to be important in medicinal chemistry and have had a significant impact from both an industrial and biological standpoint [12]. Two of the six atoms in the ring structure of the pyrimidine structure are nitrogen atoms. But they don't really exist in nature. They are found as derivatives instead. It has three isomeric diazines and is a component of both DNA and RNA, which explains its many biological functions [13]. The term "pyrimidine," which is a combination of the terms "pyridine" and "amidine," was created by Pinner [14]. Fused pyrimidines are pyrimidines that have fused with other heterocyclic rings. Purine is an example of a fused pyrimidine that exhibits a wide range of biological activity [15]. Most organisms use the de novo pyrimidine synthetic pathway to produce pyrimidines, while the remaining organisms use the Uracil salvage pathway [16]. The minimal π electron density of pyrimidines is larger than that of pyridine molecules. This explains why electrophilic aromatic substitution is more difficult than nucleophilic substitution of pyrimidines. Only one of the pyrimidine's nitrogen rings undergoes protonation or alkylation. Pyrimidines also have a lower basicity, or lone pair electron density, than pyridines [17].A thorough review of the literature identifies a number of pharmacological actions of substances with pyrimidine nuclei. For instance, barbiturates with pyrimidine nuclei in their structure, such as phenobarbitone, have sedative, hypnotic, and anticonvulsant effects; 5-fluorouracil also exhibits anti-cancer properties [18]. Additionally, pyrimidines disrupt the function and synthesis of nucleic acids. For instance, the anti-HIV medication zidovudine inhibits the nucleoside reverse transcriptase enzyme and has the pyrimidine pharmacophore [19]. The pyrimidine pharmacophore is also responsible for the effectiveness of the antibiotics fervenulin and hexidine [20]. As possible bioactive compounds, pyrimidines fused with other heterocycles are highly valued. These combined substances exhibit antiviral, antidepressant, anticancer, and antioxidant properties.For example, medications with antipsychotic properties, like mezilamine and risoperidone, are used to treat schizophrenia, irritability associated with autism, etc. [21]. The chemistry of fused pyrimidine moieties [22], the most important of which are purines and pteridines [23], began when Scheele isolated uric acid in 1776.Leucopterin [26], isoxanthopterin [25], and xanthopterin [24] are a few naturally occurring pteridine derivatives that are found in butterfly wings. From a medical perspective, riboflavin, which is prescribed to treat vitamin B2 deficiency, has a pteridine ring [27]. Triamterene, a chemical known as 6-phenylpteridine-2,4,7-triamine, has been effective in treating edema brought on by liver cirrhosis and congestive heart failure [28]. Further investigation of fused pyrimidine derivatives is considered important due to their significance in other fields, including antithrombotic, antiplatelet, and anti-cancer medications [29].

A technique for functionalizing the Heterocyclic nucleus has important applications in the synthesis of natural products and medicinal chemistry [30–31]. β-keto amides, particularly acetoacetanilides, have recently been investigated as a readily accessible, structurally adaptable, and versatile starting material in chemical synthesis for the creation of complex molecular systems with a variety of functionalities [32]. Under green reaction conditions, we intended to functionalize the pyrimidine nucleus in this context by reacting acetoacetanilides with aldehydes and urea/thiourea.

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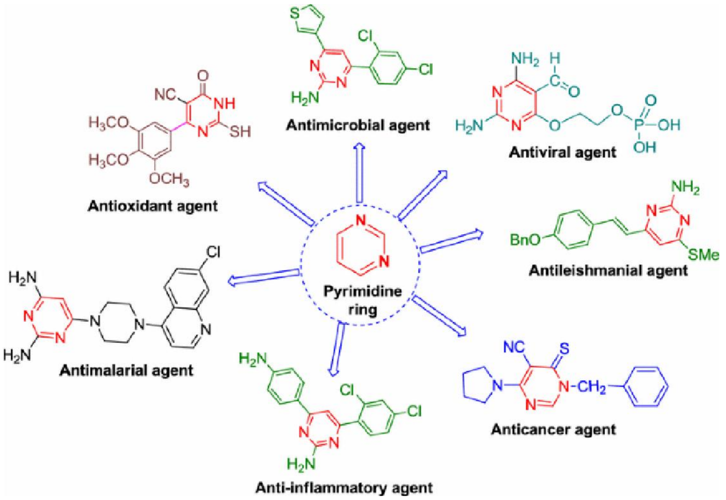
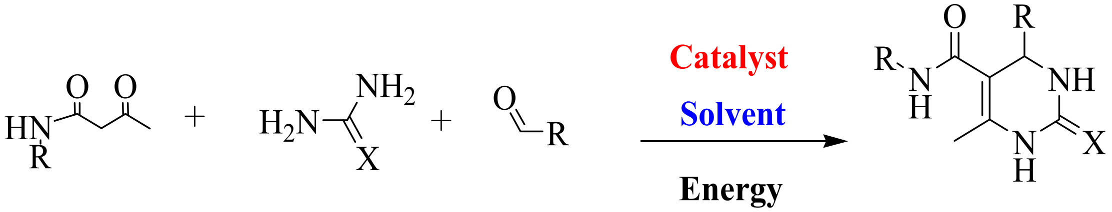


Figure 1: Representative Examples of Pyrimidine framework present in different compounds

II. RESULTS AND DISCUSSION

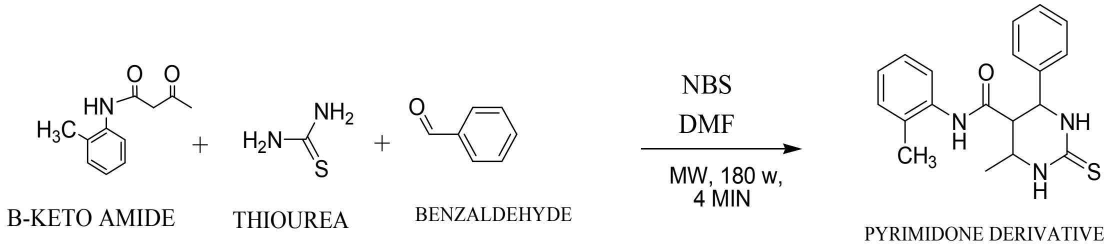
We started our work with the reaction of one mol of β-keto amide and 1 mole of Thiourea and Benzaldehydeunder different reaction conditions (Scheme 1).However, we observe that, the reaction was possible and provided the desired product of Pyrimidine derivative in good yield, when we used N-bromosuccinimide (NBS) as catalyst& N.N. dimethylformamide (DMF) as a solvent under Microwave Irradiation Heating.For initial optimization of the reaction conditions, we tested several protic acids and Lewis's acids, and found the N-bromosuccinimide (NBS) gave the best results. Stronger protic acids also served as catalysts, but the yields were relatively low. When stronger protonic acids a were used, the reaction mixtures became dark-brown and many byproducts were generated. Furthermore, Lewis's acids likealuminium chloride and zinc chloride were not efficient catalysts for this reaction.



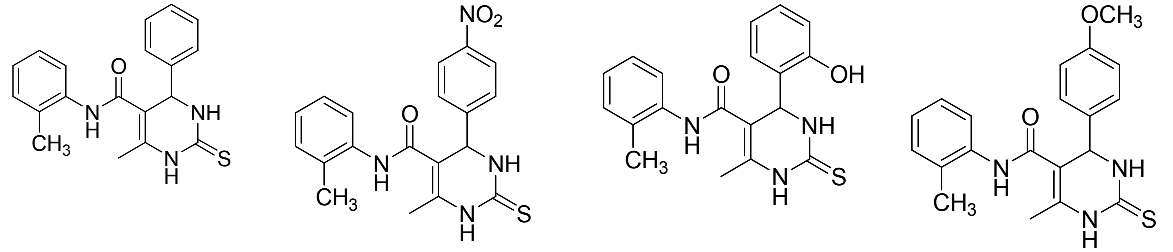
Scheme 1: Optimization of Reaction Condition for the synthesis of Pyrimidine derivative.

As N-bromosuccinimide (NBS) proved to be the most effective acid, further experiments were focused on the screening of solvents. When different non-polar solvents were used the yield of reaction was very poor due to less solubility of reactants in these solvents. The conversions were much low when the reactions were carried out in organic solvents like Toluene. In all kinds of the tested solvents, N.N. dimethylformamide (DMF)gave the best results. Herein, we performed the further study in N.N. dimethylformamide (DMF) solvent. We have also tested the effect of Microwave Irradiation in this reaction. We tested the reaction of one mol of β-keto amide and 1 mole of Thiourea and Benzaldehyde with N-bromosuccinimide (NBS) as catalyst& N.N. dimethylformamide (DMF) as a solvent under Microwave Irradiation Heating of different Power for different time. We observed the best result when, we performed the reaction of one mol of β-keto amide with1 mole of Thiourea and Benzaldehydein the presence of N-bromosuccinimide (NBS) as catalyst& N.N. dimethylformamide (DMF) as a solvent under 180 w powers of Microwave Irradiation for 4 minutes (**Scheme 2**). Hence, we selected the reaction of one mol of β-keto amide with1 mole of Thiourea and Benzaldehydein the presence of N-bromosuccinimide (NBS) as catalyst& N.N.

dimethylformamide (DMF) as a solvent under 180 w powers of Microwave Irradiation for 4 minutes as a optimized reaction condition for the synthesis of different Pyrimidone derivatives (**Scheme 3**).



Scheme2: Synthesis of Pyrimidone derivative under Optimized Reaction Conditions.



1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxo-N-o-tolylpyrimidine-5-carboxamide

1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-thioxo-N-o-tolylpyrimidine-5-carboxamide

1,2,3,4-tetrahydro-4-(2-hydroxyphenyl)-6-methyl-2-thioxo-N-o-tolylpyrimidine-5-carboxamide

1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-thioxo-N-o-tolylpyrimidine-5-carboxamide

Scheme3: Structures of four different Pyrimidone derivativesynthesized under Optimized Reaction Conditions.

General Procedure: Place equal moles of β-keto amide (1 mmol) Thiurea (1 mmol) & Aldehyde (1 mmol) in 100 ml Beaker. Add N-bromosuccinamide (0.025 g.) as catalyst. & N.N. dimethylformamaide (4ml) as a solvent, mix well clear solvent obtain.Place this reaction mixture in micro wave own at 180 powers for 4 min. The progress of reaction was checked by TLC. After 4 minutes, a brick red color solution is formed which is then allowed to cool, & pour this reaction mixture in to cold distilled water.White Coloured solid precipitate was formed which was then filtered & dried. The obtained crude product was further purified by chromatography on silica gel using EtoAc:Hexane, 20:80 as an eluant, and dried to afford product as a white solid. The pure product was confirmed by different techniques and identified as desired Pyrimidone compound.

Spectral Data:1,2,3,4-tetrahydro-6-methyl-4-phenyl-2-thioxo-N-o-tolylpyrimidine-5-carboxamide White solid, yield 92%, mp 222-224 °C, ^{1}H NMR (400 MHz, DMSO-d6) 1H NMR (300 MHz, DMSO-d6): δ 8.18 (br S, 1H), 6.65-7.88 (m, 9H), 3.76 (br S, 3H), 2.33 (s, 3H), 1.81 (s, 3H) ppm

III. CONCLUSION

In conclusion, we have developed Microwave assisted rapid, convenient and efficient method for the exclusive synthesis of functionalized pyrimidine derivative framework under metal-free condition. This functionalized β-keto amide used to afford new diversely functionalized pyrimidine Derivative structural framework. This method is a straightforward route for the for the regioselective and Chemo-selective addition of β-keto amides on aldehyde followed by reaction with thiourea to afford functionalized pyrimidine Derivative. The developed procedure includes the reaction of one mol of β-keto amide with 1 mole of Thiourea and Benzaldehyde in the presence of N-bromosuccinamide (NBS) as catalyst & N.N. dimethyl formamaide (DMF) as a solvent under 180 w powers of Microwave Irradiation for 4 minutes to afford the desired Pyrimidone Derivatives. Moreover, the method affords the high yields of the desired product under mild reaction condition from readily available starting materials. Additionally, this method is applicable for a variety of functionalized aldehyde as well as β-keto amides and thiourea. The obtained diversely functionalized β-keto amides framework is amenable for further structural manipulations, hence can be useful for the synthesis of natural products and a library of new pharmaceutically important molecules.

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