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Alternative Methods in Heterocyclic Synthesis Based on Green Chemistry

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Abstract

The foundation the application of state-of-the-art scientific methods to address environmental issues that occur during laboratory experiments. The chapter 1 will provide introduces the topic, and Chapter 2 reviews the literature on the topic of synthesis and its applications of a few major classes of heterocyclic compounds. In Chapter 3, we go deeply into all twelve of Paul Anastas's 1991 Principles of Green Chemistry. Our focus is on the medicinal chemistry processes used in labs to prepare APIs. This article offers a guide to making reactions more environmentally friendly and suggests alternative, environmentally friendly responses that might replace the tactics used by businesses and universities. Chapter 4 will detail the primary thioamide and selenoamide dimerization mediated by tert-butyl nitrite and chloranil-, respectively, as methods for synthesizing 1,2,4-thiadiazole and 1,2,4-selenadiazole. Also included is an easy-to-follow process for making azide[1,2-a] pyridines when left alone using a KI/TBHP catalytic system, without the need for solvents or metals. and chapter 5 Here, we examine some methods that medicinal chemists can employ to improve both the environment and human health: boosting yields while reducing or eliminating pollution.

Keywords: Ecologically, favorable, Green Chemistry, medicinal, industrial

Introduction

The use of less harmful, ecologically favorable solvents in favor of traditional, potentially harmful ones is a fundamental tenet of Green Chemistry. More and more, non-conventional solvents including water, ionic and fluorous liquids, supercritical media, and mixtures of these are finding use in scientific research. Catalysis is still a major area of Green Chemistry since it solves several key industrial issues in an energy-efficient, selective, and atom-cost-effective method.

Improved selectivity, softer the manipulation-friendly reaction conditions and potential people are interested in inorganic 3,4 solid-supported reagents because of its possible uses. Researchers are keen in microwave heating for its ability to enhance product yields, decrease reaction times, and make reactions more selective in techniques requiring high temperatures and extended durations. Microwave Radiation (MWR) Administration 5-8 in chemical synthesis has increased during the last decade. Typically, the research is conducted using microwave ovens of the home kind or instruments designed for sample preparation and analysis (digests). There is now microwave apparatus 9–11 that is specifically designed to conduct organic processes. Among the scaffolds found in pharmaceutically significant chemicals and medications, heterocycles are among the most common. Due to their drug-like nature and wide structural variety, heterocycles are often used in early phases of drug development programs for high-throughput screening. Thus, this study aims to show how the following heterocyclic compounds may be synthesized in accordance with green chemistry principles.

Basic Principles of Green Chemistry

An all-encompassing framework for developing chemical processes and products that are ecologically and socially responsible may be found in the Twelve Principles of Green Chemistry20-22. Preventing waste from occurring in the first place is emphasized in the first principle. Second, atom economy promotes resource efficiency by reducing wasteful by-products and over-consumption of basic resources. The need to develop procedures that use materials with minimum toxicity to people and the environment is emphasized by the third principle, less hazardous chemical

syntheses. The goal of the fourth principle, "designing safer chemicals," is to produce useful chemical products with as little risk of damage as possible. The fifth principle, which is to employ safer solvents and auxiliary, necessitates the use of non-toxic auxiliary compounds that won't hurt people or the environment. The optimization of processes to decrease energy consumption, preferring circumstances of ambient temperature and pressure, is the sixth principle of energy efficiency design. The seventh principle encourages using renewable feedstocks as a source of sustainable and replenishable raw materials. The eighth principle is to decrease derivatives., and it encourages keeping derivatization procedures to a minimum since they add to waste.

In order to improve reaction speeds, decrease energy consumption, and limit by-products, the ninth principle suggests using catalytic reagents instead of components of a stoichiometric reaction. The tenth principle is to make chemical products with the intention that they would degrade over time. after their useful life is up, decompose into harmless byproducts, so they don't end up all throughout the world. Eleventh principle: monitoring pollution levels in real-time avoidance promotes in-process monitoring analytical procedures to avoid the generation of harmful compounds. The twelfth principle, which advocates for "inherently safer chemistry" in the interest of accident avoidance, recommends using materials and construction methods that lessen the likelihood of chemical mishaps. Creating chemical procedures that are less harmful to humans and the environment and products may be advanced by following these principles, which serve as a roadmap for researchers and industry experts to incorporate sustainability into their activities.

A key component GC involves drastically cutting down on, or doing away with entirely, any hazardous chemicals throughout the synthesis process. As a result, less or no harmful compounds that endanger human and environmental health are used. While it would be unrealistic to try to include all of the GC method's concepts into the design of a process all at once, the method's use at some phases of synthesis has shown promise.

1. The design of degradation processes, the creation of less harmful chemicals, and the avoidance of waste and by-products
2. Using non-traditional biotech solutions.
3. No synthesis requires more energy than necessary
4. Prevention or reduction of harmful substances
5. Avoid using the group's protection mechanism whenever you can.
6. It is preferable to avoid derivatization wherever possible.
7. Choosing the right catalysts, reagents, and solvents.
8. To be acknowledged as industrial procedures, the use of novel techniques is essential.
9. A high rate of reactant and reagent integration into end products.
10. To reduce toxicity while preserving efficacy, chemical compounds should be devised.
11. Energy needs should be acknowledged in order to reduce their economic and environmental implications.
12. Whenever possible from a scientific and financial standpoint, raw materials should be renewable rather than diminishing.
13. Chemical substances should be engineered such that they decompose transform into harmless byproducts of breakdown and disappear from the environment.
14. Prior to the production of harmful substances, analytical processes should be established to enable real-time procedure examination and control.
15. Create production facilities that will reduce or eliminate the possibility of mishaps occurring during the escalation of analytical procedures for the control of harmful substances.
16. Use and formation of a substance that produces little to no negatively impacting both human and environmental health need to be the objective of synthetic operations wherever possible.
17. To reduce the likelihood of chemical mishaps, explosions, and fires, it is important to choose substances for chemical processes with care.

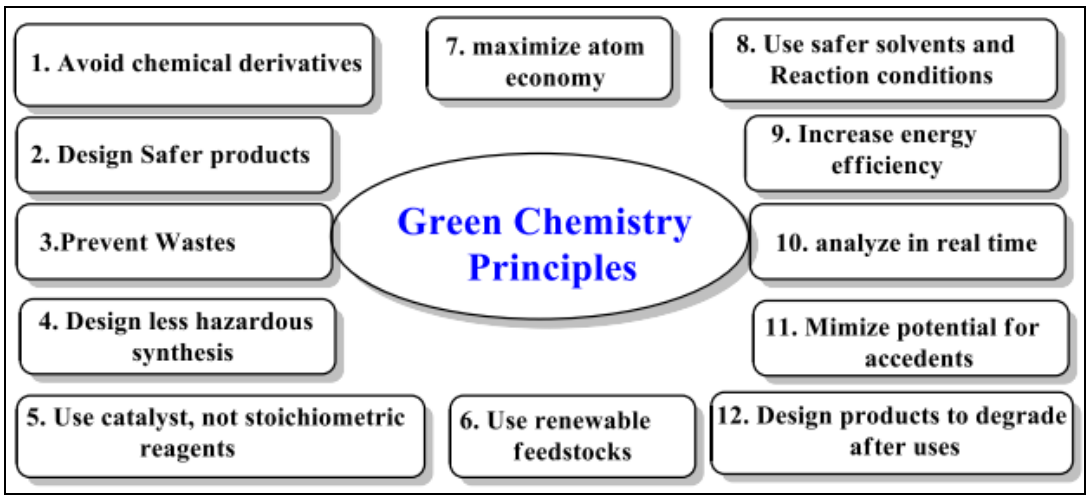


Fig 1: Principles of Eco-Friendly Chemistry

Literature Review

Abdellah, Islam & Eletmany, Mohamed. (2024) [2]. This extensive study delves into the latest achievements in green chemistry, specifically looking at how poly-heterocyclic molecules may be synthesized in water utilizing microwave (MW) irradiation. Decreases in chemical byproducts and

reaction times have resulted from the implementation of ecologically friendly practices that use greener alternatives. Heterocyclic hydrazones, tetrahydropyrans, dihydropyrimidinones, triazoles, cyclic ureas, and oxygen heterocycles are some of the approaches highlighted in the review. Modern methods such as alkylation of nitrogen, direct addition of the Grignard type, and condensation of three components processes allow for the production of many heterocyclic structures. Some of the benefits include faster response times, increased product outputs, and the removal of dangerous organic solvents. benefits highlighted in the study. The techniques are environmentally benign since they employ recyclable catalysts such nano-sized magnesium oxide and montmorillonite K10 clay. Sustainable and efficient synthetic procedures are shown by using green synthesis concepts, such as water-mediated conditions and catalyst recyclability. As the area of heterocyclic compound synthesis continues to advance, this study sheds light on the continuing efforts to lessen the toll that chemical synthesis has on the environment.

Asif, Mohammad & Ansari, Mohd. (2021) [4]. Many challenges arose for those engaged in the creation of green chemistry. of medical, education, and research that use chemistry. A revolution in response to the desire to lessen the harm that synthetic chemicals and their production processes do dangers to ecosystems and people's well-being, "green chemistry" emerged in response. Using gentle, non-toxic, environmentally friendly, and easily reproducible catalysts and solvents is the gold standard when it comes to green chemistry applications in the lab. New organic molecules and processes may be developed according to within the bounds of "green chemistry," an approach in an effort to mitigate harm to the natural world. According to many sources, a diverse range of heterocyclic compounds with cyclic structures, including The synthetic elements nitrogen, oxygen, and sulfur exhibit a several biological processes. A fresh perspective on the microwave irradiation synthesis of heterocyclic compounds has recently been revealed, which does not need the use of solvents and involves reactants immobilized on solid supports. The substances synthesized in this study include benzimidazoles, triazoles, oxadiazoles, benzoxazoles, and imidazole's, among others. while demonstrating the benefits of using microwave activation in a solvent-free environment. Along with "green chemistry" methods that are less harmful to the environment and make use of low-cost, non-corrosive chemicals and reagents, there are several benefits of using microwave irradiation.

Jangale, Asha & Dalal, Dipak. (2017) [5]. This study aims to provide water, solar power, ionic liquids, ultrasonication, and other unconventional and traditional media are all part of the framework of the many and effective green approaches. One important goal in organic synthesis is the use of catalysts that are bio-based. Traditional laboratory methods may be enhanced with the use of these procedures.

Karmakar, Rajiv & Mukhopadhyay, Chanda. (2023) [6]. The remarkable biological and pharmacological actions of heterocyclic compounds make this area of organic chemistry both important and fascinating. The primary objective of contemporary organic synthesis is the development of greener synthetic techniques that are both ecologically friendly and synthetically efficient in order to synthesize fused heterocycles. We can meet the future difficulties of developing an eco-friendly synthesis framework for bioactive heterocycles that maximizes production while minimizing side products. Recent decades have seen a dramatic shift in organic chemistry as a result of new approaches to synthesizing fused heterocycles. Consequently, the primary focus of modern synthetic chemistry is on developing methods for the efficient and environmentally benign production of fused heterocycles. Methods Using environmentally friendly synthetic techniques, a variety of nitrogen and oxygen-containing fused heterocyclic compounds with bioactive properties are created. Methods such as modular, one-pot, multi-component, cyclocondensation, and cycloaddition processes are used in these tactics. The use of solvent-free reaction medium, green solvents, and procedures supported by ultrasound and microwaves are all important steps towards increasing sustainability. This work seeks to demonstrate the potential for environmentally friendly approaches to produce bioactive fused heterocyclic molecules that include nitrogen and oxygen. The goal is to help academics and industry members find and implement synthetic processes that are both economically and environmentally viable. To summarize This study has gone over the most recent innovations in green synthesis techniques for bioactive fused heterocyclic compounds based on nitrogen and oxygen, which are going to hopefully spur further studies in this area.

Rao, Nishanth & *et al*. (2021) [1]. According to the US retail market in 2014-2015, Eighty percent of all commercial drugs are based on heterocyclic moieties. On the other hand, there is a need for environmentally benign strategies as many synthetic processes cannot be sustained. For instance, microwave-assisted synthesis allows for the rapid, efficient, and energy-efficient synthesis of compounds with high yields using very little energy. Similarly, nanoparticles doped with metals provide benefits in synthesis that use nanoparticles, such as a recyclable catalyst, high yields with rapid responses. Additional environmentally friendly approaches include synthesis without solvents, synthesis using combinatorial techniques, sonochemistry-assisted synthesis, organic synthesis in water, and ionic liquid-assisted synthesis. We examine solvent-free synthesis, conventional synthesis, and organic synthesis in water., the three main approaches to organic synthesis. in conjunction with microwave irradiation. Using nanoparticles as catalysts, we demonstrate the production of complex heterocyclic compounds. Green features of synthetic methods are our main focus.

Green chemistry approaches attempt to reduce waste and use safe chemicals for humans and the environment

Reagent Guides to Improve Greenness

The safety of chemical intermediates and end products has been the focus of several initiatives up to this point. Pharmaceutical giants Pfizer and GSK collaborated to create the Reagent Selection Guide, an invaluable resource for medicinal chemists in their pursuit of optimal product synthesis. this approach enables chemists to replace troublesome reagents according to certain criteria.

When ranking the well-established reaction conditions, "greenness," "scalability," and "wide utility" are used. The

central green region indicates perfect reagents with all three features, whereas the other reagents might have two features but not the third or only one. Solvents, catalysts, and waste management are only a few of the variables that decide where each circle goes. Additionally, each reagent is connected to its corresponding reference in the online edition of this guide, which helps to improve understanding of newly developing green techniques via the essential literature. Subsequently, Environmental Task Force of the American Chemical Society's Pharmaceutical Discussion Group Chemistry Institute received the handbook as a donation for the purpose of developing and expanding it.
The Reagent Selection Guide's ketones from secondary alcohol oxidation published by Pfizer.
The Oppenauer oxidation offers an environmentally friendly option for this process, The discovery of this reaction in 1937 made it a green option; the base and only by-product are stoichiometric amounts of aluminum catalyst is isopropanol.

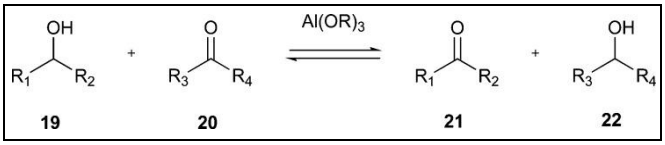


Fig 2: A generic plan for the oxidation of secondary alcohols by Oppenauer.

The pharmaceutical company GSK has implemented a strategy to incorporate sustainability into routine practice and offer a more environmentally friendly substitute for the most used reagents throughout the process of creating new medications. A new environmentally friendly method of oxidation via NaOCl has been developed by the business for nitrosyl radical catalysts like TEMPO and PIPO. Nevertheless, because of their low atom economy, these oxidants are unsuitable for reactions on a broad scale. The guide aims to incorporate sustainability into routine practice and offer a more environmentally friendly substitute for the most used reagents. The guide-listed ratings are based on a comprehensive evaluation of all relevant variables and chemical factors. Each reagent is given a color, with green representing minimal concerns, yellow for some difficulties, and red for substantial issues, to make the guidance easily understandable. The GSK reagent guide is one example of this approach.

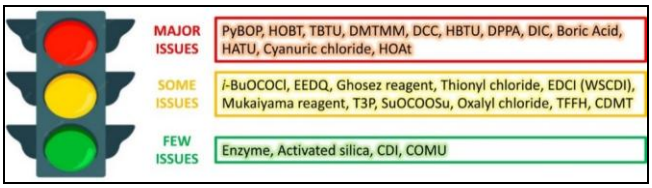


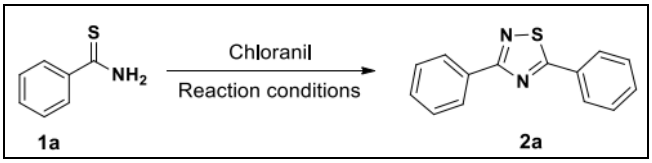
Fig 3: Amide synthesis in accordance with the GSK reagent protocol suggested by Adams *et al.*

Synthesis of heterocyclic compounds

Enhancing reaction perception with chloranil

The next step in optimizing the reaction conditions was to use chloranil and thiobenzamide in equimolar proportions (1a). Following that, three hours of stirring in room temperature water, only 20% of product 2a was yielded.

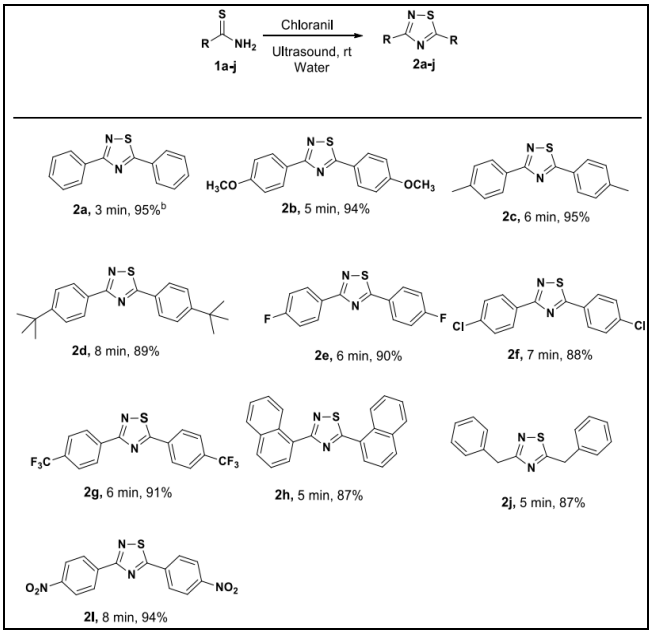
Table 1: Variation in model compound 2aa yield as a function of reaction circumstances



Entry	Reaction conditions	Solvent	Time	Yield' (%)
1	Stirring, rt	H_2O	3 h	20
2	Stirring, reflux	H2O	3 h	40
3	50 °C	Solvent-free	3 h	50
4	80 °C	Solvent-free	3 h	70
5	120 °C	Solvent-free	3 h	70
6	Ultrasound (US), rt	H_2O	3 min	95
7	US, rt	MeCN	5 min	75
8	US, rt	THE	10 min	70
9	US, rt	Et0H	15 min	85
10	US, rt	1, 4-Dioxane	12 min	65
11	US, rt	$CHC1_3$	8 min	78
12	US, rt	CH_2C1_2	9 min	79
13	US, rt	DCE	7 min	82
14	US, rt	DMSO	10 min	78
15	US, rt	PhH	12 min	71
16	US, rt	PbMe	15 min	75

an Ingredients for the reaction: 3 milliliters of solvent, 1.1 millimethyl chloranil, and 1.0 millimol of thiobenzamide.

Table 2: Synthesis of thiadiazoles derivatives 2a–j[a]

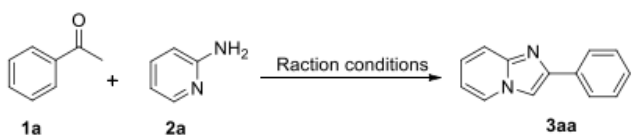


Results and Discussion

The model substrates to be employed with KI/TBHP were acetophenone (1a) and 2-aminopyridine (2a), in order to optimize the reaction conditions. Experimental variables included solvents, reaction temperatures, catalyst loadings, and reaction times. The polar solvents were the only ones that allowed the stirring experiment indicated that the reaction would occur at room temperature with a poor yield. When looking at product yield, we discovered that ethanol was the best polar solvent to use. Table 3, entries 1-12, shows that no reactions occur when non-polar solvents are

used. Table 3, entry 13 shows that after one hour of increasing the product yield in a solvent-free environment at room temperature, the results revealed a 65% yield. The subsequent impact of temperature was examined. According to Table 3, entries 14, and 15, there is little to no change in the product yield when the temperature is increased up to 80 oC during stirring. One environmentally friendly method is grindstone chemistry, which may be used to synthesize various chemicals. This being considered, the reaction was carried out for a certain amount of time while subjected to the grinding condition and KI/TBHP. Table 3, entry 16 shows that a 5-minute reaction produced a 70% yield, while entry 17 shows that an 8-minute reaction produced an 80% yield. Obtaining a 95% product yield in under 10 minutes was a pleasant surprise (Table 3, item 18). Additionally, there is no significant difference in product yield when the duration is increased up to 15 minutes (Table 3, item 19). On top of that, the concentrations of the catalyst and oxidant were adjusted. Since no product was produced without KI (Table 3, item 20), we have begun optimizing the catalyst KI with 1 equiv. of TBHP. Then, after 10 minutes, we achieved a 75% yield (Table 3, entry 21) an increase of 0.2 equiv of KI in the amount. By increasing the amount of KI to 0.5 equiv., we were able to attain a 95% yield in about 10 minutes (Table 3, entry 18).

Table 3: Amino acid [1,2-a] reaction optimization organic compounds



Entry	Solvent	Catalyst/TBHP (Equiv.)	Reaction condition	Time (Min)	Yield[b] (%)
1	Ethanol	KI (0.5)/ 1	Stirring / it	60	50
2	Methanol	KI (0.5)/ 1	Stirring / it	60	50
3	Water	KI (0.5)/ 1	Stirring / rt	60	40
4	DMSO	KI (0.5)/ 1	Stirring / rt	60	20
5	1,4Dicocane	KI (0.5)/ 1	Stirring / it	60	20
6	THE	KI (0.5)/ 1	Stirring / rt	60	15
	Chloroform	KI (0.5)/ 1	Stirring / rt	60	10
8	DCM	KI (0.5)/ 1	Stirring / rt	60	12
9	Toluene	KI (0.5)/ 1	Stirring / rt	60	No reaction
10	Xylene	KI (0.5)/ 1	Stirring / rt	60	No reaction
11	Hexane	KI (0.5)/ 1	Stirring / rt	60	No reaction
12	Benzene	KI (0.5)/ 1	Stirring / rt	60	No reaction
13	Solvent free	KI (0.5)/ 1	Stirring / rt	60	65
14	Solvent free	KI (0.5)/ 1	50 °C	60	70
15	Solvent free	KI (0.5)/ 1	80 °C	60	70
16	Solvent free	KI (0.5)/ 1	Grinding/rt	5	70
17	Solvent free	KI (0.5)/ 1	Grinding/rt	8	80
18	Solvent free	KI (0.5)/ 1	Grinding/rt	10	95
19	Solvent free	KI (0.5)/ 1	Grinding/rt	15	96
20	Solvent free	KI (0.5)/ 1	Grinding/rt	15	No reaction
21	Solvent free	KI (0.5)/ 1	Grinding/rt	10	75
22	Solvent free	KI (0.5)/ 1	Grinding/rt	15	95
23	Solvent free	KI (0.5)/ 1	Grinding/rt	15	No reaction
24	Solvent free	KI (0.5)/ 1	Grinding/rt	15	95
25	Solvent free	KI (0.5)/ 1	Grinding/rt	25	80

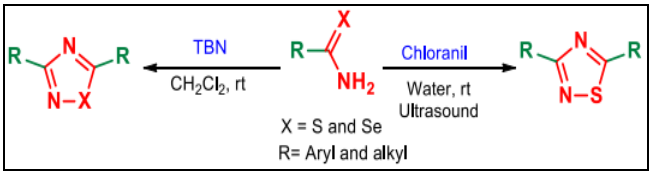
Included in this set of reaction conditions are KI, an oxidant TBHP, 2-aminopyridine (1.2 mmol), acetophenone (1.0 mmol), and their separated yields.

Conclusions

The inseparability of the principles is an additional point that we have previously brought up on several times. In addition, we have reviewed a few of the principles thus far in an effort to bring them together and highlight their key aspects. So, as shown in the review image, we laid down the seven fundamental principles, which include things like harmless chemicals, energy efficiency, safety, reducing derivatives, analysis, and reduction of derivatives. They combine into what is known as "green chemistry" and serve as a daring basis. In the same way as white encompasses every color green chemistry incorporates all seven principles, much like the colors of the rainbow. What are some possible possibly be more contrasting than a black backdrop, as is used in "classical" (medical) chemistry, to make a rainbow even more visible?

Since the concepts are already accessible, it is imperative that all (medical) chemists apply the tenets of environmentally friendly chemistry.

"Green Approaches for the Synthesis of Some Biologically Relevant Heterocyclic Compounds" is the title of the thesis that covers the environmentally friendly ways to synthesize heterocyclic compounds that include sulfur, nitrogen, and oxygen. These chemicals are crucial for biology. Various analytical experimental approaches, including 1H and 13C Analysis of elements, the use of nuclear magnetic resonance, FTIR spectroscopy, and MS, have been used to characterize the produced compounds. offers an overview of the field as a whole as well as a literature review on the topic of the synthesis and applications of a number of primary classes of heterocyclic compounds comprising nitrogen, oxygen, and sulfur. discusses in depth the two-step 2,4, -thiadiazole and 1,2,4-selenadiazole synthesis. At room temperature, radical dimerization of initial thioamides and selenoamides was induced by tertbutyl nitrite, allowing for thorough synthesis. Additionally, primary thioamides were effectively forced to dimerize under metal and catalyst free conditions by chloranil-mediated ultrasound. In a very short amount of time, the created techniques provide good to exceptional yield while being easy to use and efficient. Method A.



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