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Green Chemistry Approaches in Hydrogenic Synthesis

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Abstract

The presence of heterocyclic compounds in vitamins, hormones, medicines, and pigments highlights their widespread presence in nature and their significant impact on human existence. An abundance of sulfur-, nitrogen-, and oxygen-containing heterocyclic compounds exhibit biological activity and serve as crucial components for the synthesis of molecules that organic chemists find intriguing from a biological or medical perspective. Heterocyclic compounds like the most important ones include 4-H pyran, thiadiazoles, coumarin, and imidazo[1,2-a] pyridines. building blocks of some physiologically important moieties. Thesis topics include "Green Approaches for the Synthesis of Some Biologically Relevant Heterocyclic Compounds" and their diverse methods of synthesis. Many businesses and academic institutions are now concentrating on green chemistry. Reducing reaction temperatures while increasing reaction speeds is an important objective of "green chemistry," which also seeks to find more ecologically friendly reaction conditions. By implementing targeted, long-term initiatives, "green chemistry" aspires to lessen chemical exposure and its negative effects on human health while simultaneously eradicating pollution from the environment.

Keywords: Developments, Environmentally, growth, production, Green Chemistry

Introduction

"Human beings are at the Centre of concerns for sustainable developments-they are entitled to a healthy and productive life in harmony with nature" is According to the Rio Declaration's first principle, "sustainable development," we are all faced with the task of defining and achieving this goal. Environmentally friendly growth seeks in order to lessen the negative impact of the chemicals that we use and manufacture.

For the future production of energy, chemicals, and materials to be safer for the environment than the one we have now, chemistry plays a key role. Chemical processes and products that are kind to the environment are in high demand across the globe., there is an immediate need for creative and economical methods of lowering pollution levels. The term "Green Chemistry" describes an approach to chemical product design, manufacturing, and use that seeks to reduce or do away with chemical use by using known carcinogens. Regarding environmentally friendly chemistry, it is among the most alluring concepts. Keep in mind that the rapid increase Recognizing the long-term cost-effectiveness of environmentally sensitive goods and activities gave rise to the notion of Green Chemistry.

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.

Green Chemistry

"Green chemistry" refers to approaches to chemical product and process design that aim to minimize or eradicate the production and use of harmful compounds. For the last 30 years, "green chemistry" has been making real strides

toward a more sustainable future. Significant changes in how we use energy and resources are required for a society to progress towards sustainability, which has been widely anticipated. Trans materialization and dematerialization are two sides of the same coin that must happen for scarce resources to be used effectively. Changing from using resources that are harmful and non-renewable to using resources that are safer and/or renewable or recyclable is known as trans materialization. Chemical, physical, and toxicological characteristics that enable safe handling and disposal should characterize forthcoming compounds and advancements. To this end, green chemists have developed a framework of principles and measurements that, when applied to chemical and process design, should lead to less environmental impact. If green chemistry is to realize its full potential, a coordinated revolution in several spheres of society, government, economy, and technology is required. This view promotes the development of new technologies that embody sustainability ideals via multidisciplinary design and advancement.

When it comes to synthesizing potential scaffolds, Green Chemistry is all about finding more efficient ways to do chemistry while also minimizing adverse consequences on ecological systems and human well-being. This includes using biodegradable catalysts and solvents and raw materials sourced from renewable sources [1]. Green chemistry is a very effective strategy for lowering pollution levels because it provides a systematic, creative answer to a real-world environmental problem. Research into "Green Chemistry" has become an active field of study, and this has prompted the development of novel environmentally friendly technology and the enhancement of current chemical processes to reduce their environmental impact. Twelve principles were laid down by P. Anastas and J. C. Warner in their work on Green Chemistry. In "Green Chemistry" manufacturing, toxic chemicals and solvents are not used; instead, renewable raw materials are prioritized, and waste is minimized or eliminated altogether. A new area of chemical synthesis known as "green chemistry" has recently grown in prominence, with support from both the chemical industry and universities. Despite that, Green Chemistry has brought together environmental protection and human wellness. The incorporation of green approaches, such as the building of chemical scaffolds and ecologically friendly ways for pollution avoidance, has been a major contributor to this advancement, albeit these institutions have distinct purposes. Chemists have used using the Twelve Eco-Friendly Principles of Chemistry to develop environmentally friendly processes using both traditional and unconventional materials. The need to reduce the unintentional pollution of concerns of environmental contamination and its effects on human health as a result of dangerous chemicals motivated the improvement of ideas in this context. Utilizing a variety of media such as using solar energy, ionic liquids, water, ultrasonication, and catalysts derived from biological sources, the ideas have been used in engineering organic synthesis for over a century.

Literature Review

Sharma, Suhani & Gangal, S. & Rauf, Abdul. (2008) [1]. Due to the great diversity of biological activities shown by these compounds, several papers pertaining to the synthesis of heteocycles containing nitrogen, oxygen, and sulfur have surfaced in throughout the previous many decades. A deluge of articles has been published. in recent years. detailing the synthesis of heterocycles using microwave irradiation in the absence of solvents and with reactants immobilized on solid supports. Our study focuses on the benefits and significance of using solvent-free conditions in conjunction with microwave activation for the formulating Triazines, 1, 2, 4-triazoles, benzimidazoles, benzoxazoles, 1, 3, 4-oxadiazoles, 1, 2, 4-oxazdiazoles, benzothiazoles, and imidazole's. Using non-corrosive and affordable reagents is only one of many benefits of using microwave irradiation. Other benefits include the monetary and ecological effects using safe, environmentally acceptable chemical procedures chemicals.

Farasrami, Avani. (2024) [2]. The discovery of medicinal medicines, especially when it comes to controlling type 2 diabetes, relies heavily on heterocyclic compounds. However, there are major environmental problems associated with the typical synthetic procedures for these substances since they often require hazardous reagents, non-renewable resources, and severe environments. Using harmless solvents, sustainable feedstocks, and mild reaction temperatures are some of the green chemistry concepts covered in this study, which aims to examine current developments in environmentally friendly reactions for heterocyclic molecules. These techniques improve the efficacy and safety of the produced medications while simultaneously decreasing the ecological impact of chemical synthesis. Furthermore, the article delves into the topic of how new drug delivery systems (NDDS) and creative pharmaceutical formulations might enhance the therapeutic effectiveness of these substances. It specifically highlights their potential use over the course of managing type 2 diabetes.

Suprita, & Singh, Rajvir & Sangwan, Suman & Gulati, Susheel. (2017) [3]. The advancement of environmentally friendly chemistry presented many obstacles to those working in the fields of medical, education, and research that use chemistry. In response to mounting concerns about the potential harm that synthetic materials and their production processes pose to both humans and the environment, a new field known as "green chemistry" has emerged. Synthesizing compounds using catalysts and solvents that are gentle, nontoxic, repeatable, and environmentally friendly is the gold standard of green chemistry.

Bhagat, Devidas & Chavan, Vilas & Pansare, Dattatraya & Thorat, Bapu & Shelke, Rohini & Sarkate, Aniket. (2024) [4]. The organic transformations community's focus shifted significantly toward green synthesis of bioactive heterocycles. In There has to be an urgent development of innovative eco-friendly solutions to reduce pollution's harmful effects on people and the planet. For both one-pot and multi-component synthesis, there are a number of green options available in the literature. reactions. These methods include ionic liquid, phase transfer catalyst, heterogeneous catalyst, water soluble catalyst, water mediated, and enzyme catalyzed synthesis. Many bioactive pharmaceutical medications and natural products are derived from heterocyclic structural architectures that are attached to a broad range of heterocycles with biological activities. This chapter provides a concise overview of some of the green

techniques that have been described in order to accomplish the green chemistry based on twelve principles. Recently, chemical industries have begun to apply artificial intelligence (AI) applications has skyrocketed. Artificial intelligence is useful for cataloging the many patents and articles on sustainable green chemistry. AI has significant potential in the pharmaceutical industry.

Mohammed, Tasneem & Nasreen, Aayesha & Alqahtani, Yahya & Shaikh, Ibrahim & Iqubal, Syed & Fathima, Shaik & Khan, Aejaz. (2023) [5]. Incorporating "green chemistry" practices into chemical design, production, and use reduces potential harm. This method improves energy efficiency and atom economy while decreasing environmental pollution via the use of cleaner solvents, catalysts, and reaction conditions. A great deal of harmful and undesirable chemicals, gasses, or other contaminants are being released into the environment because to the fast development of industries and cities. We need to unlock the mysteries of nature and its waste products if we want to improve and expand the synthesis of molecules with important physiological roles. Cardiovascular, antitubercular, antimicrobial, anticonvulsant, analgesic, and antitubercular actions are only a few of the many pharmacological effects that have been observed in heterocyclic compounds and their derivatives. Because of this, they have the potential to become an arsenal for treating illnesses and are excellent candidates for future pharmaceutical development. From 2002 to 2022, Eco-friendly and environmentally friendly synthetic technologies were used in a broad range. to build heterocyclic scaffolds with important physiological roles. Inspiring further progress in reaction creation within this fascinating field of inquiry, this collection of relevant material is expected to be of great relevance and practical use to organic and pharmaceutical domain chemists.

Analytical Methods for Enhancing Reaction Sustainability

Research in analytical chemistry is increasingly linked to environmental protection, with a focus on developing chemical substances, as well as methods for forecasting their usage that reduce their manufacturing and disposal. Green chemistry seeks to provide methods of evaluation that do not harm either people or the environment via the use of environmentally friendly chemicals while producing the least amount of trash possible. Think about how your designs will affect the environment choices when designing processes or product systems. To replace conventional technologies, chemists have adopted green analytical procedures throughout their analytical lifespan. Automated dilution systems are an example of green analytical chemistry, which reduces exposure and solvent use by using less solvent and product volumes. One-way green analytical chemistry can enhance the environmental effect of laboratory activities is by enhancing the sample preparation process. Reusing sample extraction instruments, introducing samples with minimal preparation, and avoiding harmful organic solvents are all ways so that we may reduce our ecological footprint and cut down on waste. Two types of extraction methods, Soxhlet and liquid-liquid extraction, are two sample preparation procedures that have been reevaluated due to their non-conformity with green analytical chemistry principles. Some more environmentally friendly extraction processes include ultrasound-assisted extraction (UAE), pressurized fluid extraction (PFE), solid-phase microextraction (SPME), also known as the GAPI, or Green Analytical Procedure Index.

$$E\text{-factor} = \frac{\text{mass of waste generated}}{\text{mass of desired product}}$$

Atom economy

It is recommended that synthetic procedures be developed in a way that allows for the maximum inclusion of all process ingredients into the end result.

The second tenet of green chemistry is to maximize material assimilation into the end product while minimizing waste and optimizing the process. It examines all available metrics for this purpose. More environmentally friendly and long-lasting methods are the result of these measures, which assess the efficiency of a generic synthetic process. For these sustainability criteria to gain global acceptance, they need to be easily quantifiable.

In recent years, the idea of atom economics has emerged as a natural progression from established metrics like product yield. This latter is how much the reactants' molecular weight is divided by how much the final product's molecular weight is:

$$\text{Atom economy}(\%) = \frac{\text{molecular weight of the final product}}{\text{total molecular weight of all reagents}} \times 100$$

AE, a chemical technique, considers every atom contributing to the final product but is only used for a single reaction step, ignoring other substances like solvents and catalysts. By cutting down on the amount of reaction steps, a step-economy strategy may improve the process's efficiency. Computer-aided organic synthesis (CAOS) can optimize the reaction's underlying mechanism while improving the atom-and step-economy. CAOS enhances reaction networks while avoiding undesired byproducts through a retrosynthetic technique. Using AE, one may determine the potential product yield while using reagents in stoichiometric proportions, without the need for experiments. AE may be used as an eco-friendly metric by estimating the efficacy of a chemical reaction according to the atomic mass and waste created. A perfect AE value is 100%.

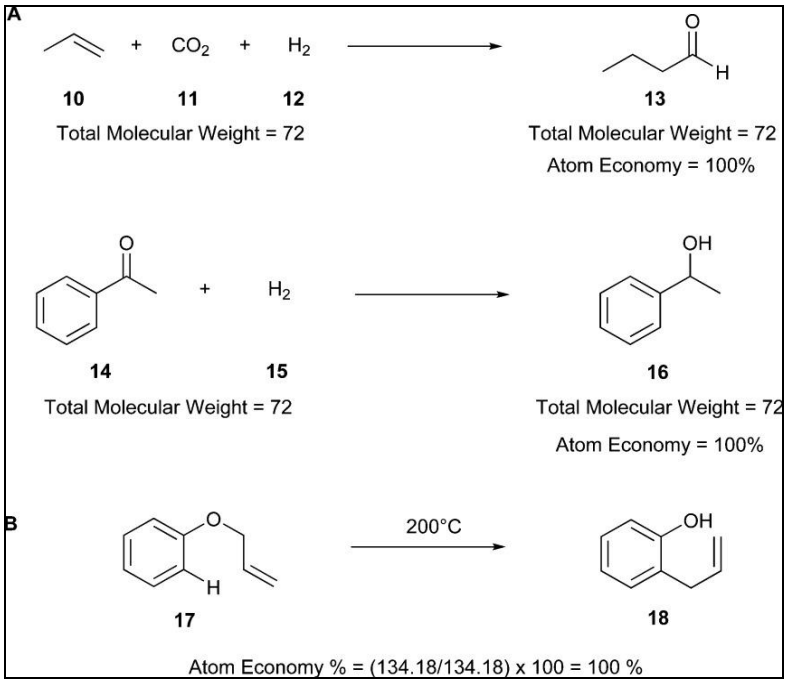


Fig 1: (A) Theoretical calculations of the atomic economy have examples. (B) The Claisen rearrangement reaction's atomic economics

Synthesis of Heterocyclic Compounds

Objective 1: Synthesis of 1,2,4-thiadiazoles and 1,2,4-selenodiazoles by the dimerization of primary thioamides and selenoamides

There has been a lot of interest in sulfur and selenium based organic compounds in many sectors in the last several decades displays the presence of 1According to a plethora of research, 2,4-thiadiazole is a major heterocyclic scaffold present in a wide variety of pharmaceuticals, medicinal chemicals, and consumer products. 1,2,4-Thiadiazoles are privileged building blocks in the synthesis of many bioactive molecules for the treatment of human leukaemia (Romagnoli *et al*. 2007) [6], as cathepsin B inhibitors (Leung *et al*. 2003) [7], allosteric modulators (Van *et al*. 2004) [8], factor XIIIa inhibitors (Leung *et al*. 2005) [9], non-ATP competitive glycogen synthase kinase inhibitors (Martinez *et al*. 2002) [10], dual 5-lipoxygenase and cyclooxygenase inhibitors (Unangst *et al*. 1992) [11]. To be more precise, drugs with thiadiazole scaffolds (Leung *et al*. 2005) [9], G-protein coupled receptors, and herbicides and fungicides (e.g., Etridiazole, Figure 1). Synthesizing organic compounds having thiadiazoles and mebendazoles moiety has remained an area of study for decades, according to various research.

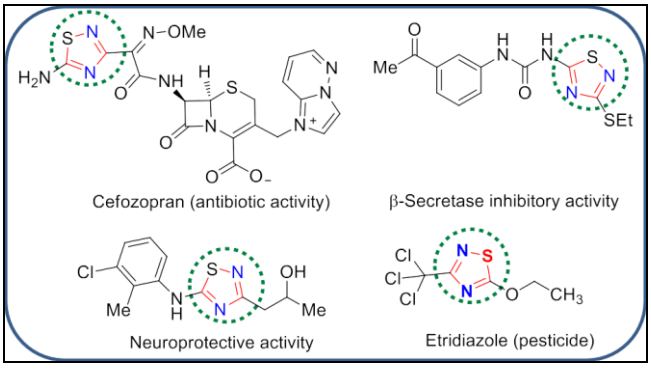
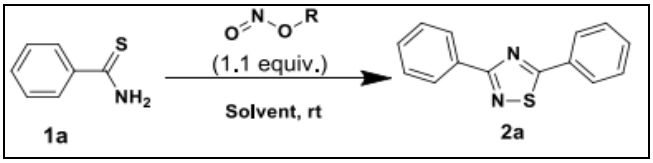


Fig 2: Biologically active thiadiazoles.

Results and Discussion

At room temperature, 1.1 equiv. of TBN was first investigated for dimerization process optimization with thiobenzamide (1a). A yield of 69% was achieved while producing the dimerized product 2a, entry 1. in acetic acid. Water, iso-propanol, methanol, tert-butanol, and iso-propanol are among the polar protic solvents that, in 30 to 60 minutes, produced the target product with a yield of 65 to 90%.

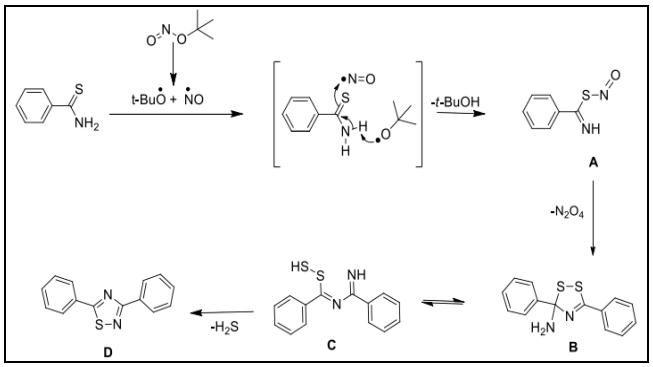
Entries 7–12 shows that dimerization was easily accomplished quickly at isopropyl alcohol, chloroform, acetonitrile, tetrahydrofuran, benzene, and toluene at room temperature. The desired compound, 3,5-diphenyl-1,2,4-thiadiazole (2a), was efficiently produced in around 5 minutes with a 95% yield, entry 7. Other alkyl nitrites, such iso-amyl nitrite (IAN) and n-butyl nitrite (NBN), were used for further optimization at ambient temperature, entries 13 and 14, show that both reagents produced the intended product in high yield, although it took a little longer-15 minutes-to complete the emotional response. The production of is indicated by the 1H and 13C NMR spectra, model compound 2a.



Mechanistic studies and control experiment

Scheme 1. shows a possible mechanism for the dimerization process mediated by TBN. When t-butoxy and nitroso radicals are produced during radical dissociation of TBN, they have the potential to combine with thiobenzamide to produce intermediate A. In addition, this intermediate has the potential to dimerize by removing dinitrogen tetroxide (N2O4), resulting in the formation of stage B, which might serve as a counterpoint to stage C. The intended end-user

item also D may be obtained by releasing hydrogen sulfide (H2S) from the intermediate C.



Scheme 1: The TBN-induced dimerization process and its proposed mechanism

Our mechanistic explanation was supported by empirical data from the dimerization process that included the 2,2,6,6-tetramethyl-1-piperidinyloxyl, and the radical trapping reagent TEMPO. At room temperature, using 2 equiv. of TEMPO in dichloromethane, the experiment was carried out under optimal circumstances (Scheme 2). Around 10% less of the target compound (3,5-diphenyl-1,2,4-thiadiazole) was detected when TEMPO was used to prevent the dimerization process, as predicted.

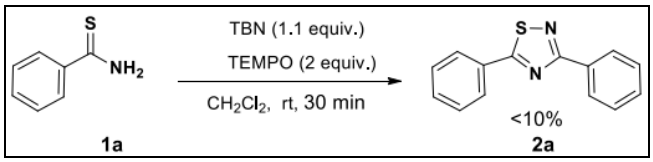
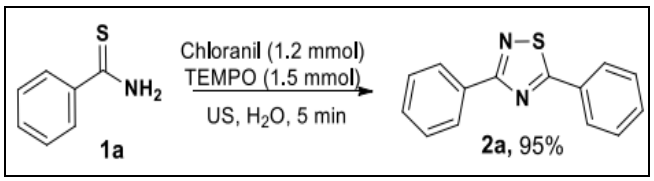


Fig 3: TEMPO control experiment.

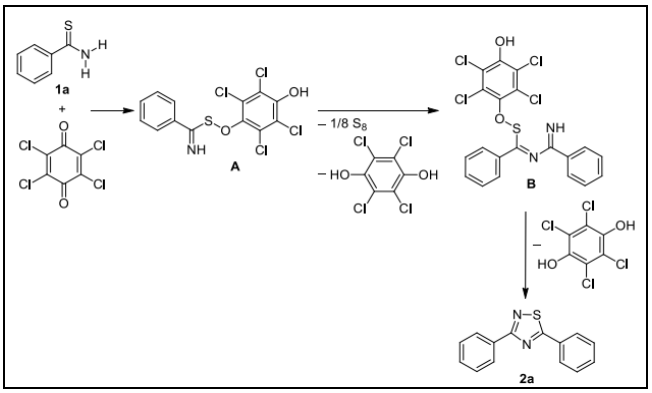
Experiments In Mechanisms and Control Using Tempo

A control experiment using (2,2,6,6-tetramethylpiperidin-1-yl) oxyl (TEMPO) as a radical trapping agent did not succeed in stopping the process. Scheme 2. proposes a nucleophilic pathway; hence this reaction does not include a radical intermediate.



Scheme 2: Experimental setup using TEMPO.

According to the findings of the product analysis, a chloranil-assisted dimerisation of primary thiobenzamide is shown in Scheme 2. Following the oxidative addition of thioamide 1a to chloranil, intermediate A dimerizes to yield intermediate B. Intermediate cyclisation B results in product 2a.



Scheme 3: The 1,2,4-thiadiazoles production pathway as proposed by chloranil.

Objective 2: Development of a scalable route for the synthesis of imidazole [1,2-a] pyridines under metal and solvent free conditions

Over the past decade, numerous studies have focused on developing methods to directly create C-C, C-N, C-S, and C-O bonds through functionalization of C-H bonds. The objective of these efforts has been to synthesize bioactive heterocyclic compounds and natural products. In a wide variety of pharmaceuticals and organic azo thiazoles, nitrogen-containing bridgehead heterocyclic compounds, useful materials pyridines are very significant groups of compounds with multiple activities, both naturally occurring and synthesized.

Researchers have focused mostly on imidazo [1,2-a] pyridines because of their many biological actions, anti-inflammatory, anti-cancer, anti-ulcer, antiviral, and antibacterial and other properties described by byth *et al*. (1999) [12] and byth *et al*. (2004) [13]. On top of that, it has been shown to engage GABA and benzodiazepine receptors and to block nonpeptide B2 receptors. An anti-HIV drug olprinone zolpidem and zolimidine are among the notable medicinal compounds comprised of heterocycles that have been discovered in recent years.

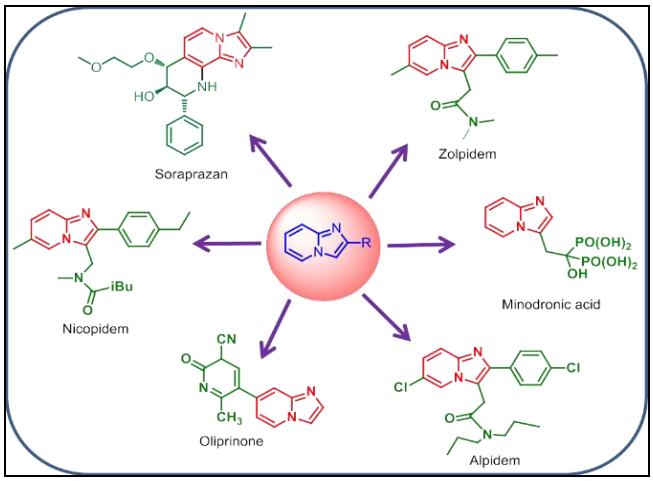


Fig 4: Medications that include imidazo [1,2-a] component of pyridines.

Due of their usefulness, Improved techniques of manufacturing imidazo[1,2-a] pyridines, which are bicyclic ring systems, have been the focus of much research. In order to create imidazo[1,2-a] pyridine scaffolds, many techniques have been devised. One of them involves reacting 2-aminopyridine with various substrates, including methyl aryl ketone, α-halo ketones, alkynes derivatives, and others. Metal catalysts such as Cu, Fe, Zn, or Ag are often used in many of these reactions (Liu *et al*., 2011; He *et al*., 2012) [14, 15]. According to the plan (4.1a). The method whereby iodine is used to produce imidazo[1,2-a] pyridine was detailed in a 2012 paper by Stasyuk. Among these steps was the presence of a base during the reaction of 2-aminopyridine with aryl methyl ketones. and the Groebke-Blackburn-Bienelayme reaction (a multicomponent reaction combining 2-aminopyridines, isonitriles, and aldehydes) have all shown the synthesis of imidazo[1,2-a] pyridine. Although these methods work well with many substrates, they do have a few drawbacks, such as requiring an acid or base, producing a poor yield, and a time-consuming workup process.

Conclusions

The widespread misconception that green(er) approaches make it harder for medicinal chemists to synthesis new compounds quickly and easily is, in our opinion, the primary explanation for the current paucity of green chemistry applications in medicinal chemistry. Therefore, sustainability and environmental friendliness are not given much thought in the lab. Medicinal chemistry experts should be aware of this growing field, and this review aims to do just that by showcasing some of the many fascinating, original, and forward-thinking approaches to drug creation that include green thinking and practices. Hence, going back to where we started, how can medical chemists help combat pollution and climate change, two of the most pressing issues of our day, and disprove the seeming contradiction between medicinal and green chemistry? To illustrate how every one of the twelve Eco-Friendly Chemical Principles may be used, we looked at many potential instances. These examples show how a synthesis route can be made greener while also improving its length, yield, safety, and, in some cases, reaction conditions. The recent meteoric rise of flow chemistry is a prime illustration of this trend. Several separation and purification processes are often skipped in this style of operation because fewer steps are involved in the response. 145 The quantity and volume of solvents and other poisonous or ecologically dangerous compounds are also dramatically reduced, which greatly improves safety.

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