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To Investigate the Highly Efficient One-Pot Synthesis of Primary Amides Catalyzed by Scandium (III) Triflate under Controlled Microwave Conditions

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Abstract:
There has been a recent shift in organic synthesis toward methods that are less harmful to the economy and the environment. In order to build the molecular structures, we want by connecting various organic species, new techniques have emerged as an indispensable tool, complementing more conventional ways. A model reaction using 2-aminopyridine and ethyl phenylacetate was used to optimize the reaction conditions. The parameters, including catalyst, oxidant, base, and solvent, were varied. The optimal solution was determined to be a CuI-K2CO3 mix in CH3CN subjected to visible light irradiation at room temperature. The reaction's viability was assessed by meticulously manipulating a model reaction involving isatin and (E)-3-(benzylamino)-3-(methylthio)-1-phenylprop-2-en-1-one, changing variables including catalyst, solvent, temperature, and molar concentration of the reactants. The second step was to conduct a few control tests to investigate the reaction pathways.

Keywords: Synthesis, Primary Amides, Controlled and Mw

INTRODUCTION

Amides are important synthetic basic materials in various areas, such as engineering, medicine, and manufacturing. Numerous bioactive substances include the amide group, which is a well-heeled chemical decoration that serves both aesthetic and practical purposes. The search for more efficient and environmentally friendly methods of amide synthesis has been an interesting area of study. Synthetic chemists are currently interested in organic transformations mediated by transition metals; so, it is important to find transition metal catalysts that are both environmentally acceptable and potentially useful in industrial settings.

A great catalyst would be one that is cheap, non-toxic, and resistant to air and moisture. We zeroed in on stable Lewis's acid catalysts because of these limitations; they're widely utilized in synthetic organic chemistry and are especially well-liked by green chemists. Allylation, aldol condensation, Diels-Alder reactions, Biginelli condensation, Ugi three-component coupling, and esterification of alcohols are just a few of the many reactions that have made use of scandium triflate's (Sc $(OTf)_3$) spectacular and fascinating catalytic chemistry. Tetrahydro pyranylation, O-glycosidation, and many other protective processes have also made use of it.

There is an immediate need to convert aldoximes to primary amides, and this process calls for very reactive chemicals. The generation of the principal amide of interest is frequently fairly poorly selective because of the presence of nitriles, carboxylic acids, and aldehydes as by-products. Generally speaking, this is considered a huge drawback for business purposes. Up until now, the conversion of aldehydes to amides has only been achieved by a few number of transition metal salts and complexes, including Rh $(OH)_x/Al_2O_3$, $[Ir(Cp)Cl_2]_2$, $Pd(OAc)_2$, $In(NO_3)_3/ZnCl_2$, $TerpyRu(PPh_3)Cl_2$, and FeCl3.36 Many people have problems with the methods that are presented. Some of these problems include extended reaction times, the use of toxic and costly metal salts or ligands, and the introduction of organic solvents that are not desired.

Literature Review

Sandeep Nivruttirao Niwadange et.al (2016) In this article, we take a look at green chemistry and its potential as a replacement for conventional organic synthesis techniques; we also provide fresh information, resources, and strategies for organic synthesis that can help the economy while also protecting people's health and the environment. In order to protect the earth from the negative impacts of organic synthesis and the many chemicals and solvents used in the process, green chemistry is becoming more important.

John M. Woodley (2019) As a result of the growing need for environmentally friendly chemicals, enzymatic catalysis is quickly making its way into the fine and specialty chemicals business, in addition to its extensive use in the pharmaceutical industry. In light of the need for efficient, scalable, and cost-effective processes that are prepared for immediate use in industry, this analysis emphasizes the growing importance of improving process performance indicators. Other cutting-edge innovations in this area, such as flow chemistry and multi-step enzymatic processes, that contribute to sustainability are also highlighted in the study.

Gopal kumar Rai et.al (2024) The field of green chemistry in pharmaceutical synthesis is seeing fast growth, with a focus on creating long-term treatments. The concepts and implementation of this novel approach in the pharmaceutical industry are examined in this research. Green chemistry reduces pollution and the usage of harmful substances by using ecologically friendly chemical processes and technologies. Reducing the environmental impact of medicine manufacturing while maintaining standards of quality and efficacy is the goal. One important part of making pharmaceuticals is using green chemistry, which involves using renewable and sustainable ingredients. By switching from petrochemical to bio-based feedstocks, pharmaceutical businesses may cut down on emissions of greenhouse gases.

Woodley, J. M. (2019) The need for more environmentally friendly chemistry is propelling enzymatic catalysis' rapid expansion into the fine and specialty chemicals business, which is already seeing extensive application in the pharmaceutical industry. This analysis emphasizes how the desire for cost-effective and scalable processes that are ready to be directly implemented into industry is driving the need for improved process performance measures. Sustainable practices are improved by further cutting-edge innovations highlighted in the study, such as flow chemistry and multi-step enzyme processes.

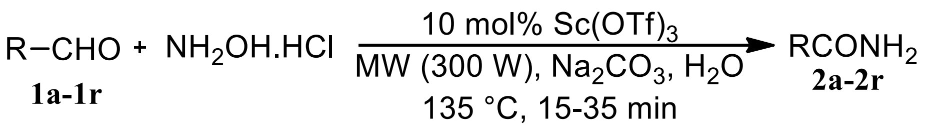
Madhuresh Sethi et.al (2018) The purpose of this chapter is to provide a business perspective on biocatalysis, with an emphasis on the pharmaceutical sector. It lays out the benefits and drawbacks of taking this route and emphasizes the necessity to bring the current chemical processes in line with the future bio-processes. We cover every single facet of what it takes to make chemical products efficiently. This is how we can change our current manufacturing practices to be more environmentally friendly. In order for biocatalytic goods to satisfy the goals of different pharmaceutical industry regulatory agencies, this chapter elaborates on how these products must be quality-controlled.

Material Method

The following ingredients were added to a 10 mL pressurized vial containing water: aldehyde (1 mmol), Na2CO3 (1 mmol), NH2OH·HCl (1 mmol, 69 mg), and Sc(OTf)3 (10 mol%, 49 mg). The vial was placed in a single-mode CEM Discover BenchMate microwave reactor and subjected to radiation at 300 W and 135 °C for 15-35 minutes after being sealed with a "snap-on" lid. The reaction was stopped once the mixture cooled to room temperature under frequent TLC monitoring. Then, three times 10 mL of EtOAc was added for extraction. After filtering, the solvent was extracted using a vacuum, and the mixed organic phase was dried over anhydrous Na2SO4. With its focus on organic reactions that are safe for both humans and the environment, "green chemistry" has emerged as a distinct field of study. Heterocyclic "drug-like" libraries may greatly benefit from the fast molecular diversity assembly using multicomponent reactions (MCRs).

Results

We provide a practical approach to the one-pot synthesis of primary amides using Sc (OTf)3 in aqueous media under controlled microwave irradiation. continuing our work on the catalytic use of transition metal salts in organic synthesis.

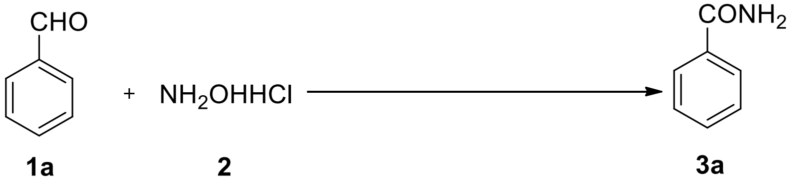


$$\underset{\mathbf{1a\text{-}1r}}{\text{R}{-}\text{CHO}} + \text{NH}_2\text{OH.HCl} \xrightarrow[\text{MW (300 W), Na}_2\text{CO}_3\text{, H}_2\text{O; 135 °C, 15-35 min}]{\text{10 mol\% Sc(OTf)}_3} \underset{\mathbf{2a\text{-}2r}}{\text{RCONH}_2}$$

Figure: 1 Sc (OTf) $_3$-catalyzed synthesis of primary amides under MW

The technique has shown its efficiency, speed, and ability to provide great yields with faster response times. Initially, we began our investigation by simulating a reaction between benzaldehyde and hydroxylamine hydrochloride in order to determine the optimal reaction parameters, including catalyst, base, solvent, MW power, duration, and temperature, under both conventional and MW irradiation. An abbreviated version of the findings is shown in Table 1. Both under traditional and microwave conditions, it is clear that there was no product when the catalyst and base were not present (Table 1, entry 1). Using reflux and 10 mol% Co (OAc)2· 4H2O /NaHCO3 in chlorobenzene resulted in a 37% yield under conventional circumstances (24 h), and a 61% yield under microwave conditions (300 W, 135 °C, 30 min) (refer to Table 1, entry 2). In the same reaction conditions, increasing the molar proportion of the catalyst Co (OAc)2·4H2O to 20 mol% resulted in a significant boost in the product yield, reaching 70% under conventional circumstances and 84% under microwave conditions (refer to Table 1, entry 3). Maximizing the concentration of Co (OAc)2·4H2O did not result in an improvement in product yield. When tested with various solvents containing Co (OAc)2·4H2O, chlorobenzene yielded the positive outcome.

Table 1 Evaluation of reaction conditions for the model reaction between benzaldehyde and hydroxylamine hydrochloride. [a,b]



1a 2 3a

Entry	Catalyst (mol%)	Base (mol%)	Solvent	Conventional Temp (°C)	Conventional Time (h)	Conventional Yield (%)	MW irradiation Yield (%)
1.	–	–	H_2O	100	24	–	–
2.	$Co(OAc)_2 \cdot 4H_2O$ [10]	$NaHCO_3$ [100]	C_6H_5Cl	135	24	37	61
3.	$Co(OAc)_2 \cdot 4H_2O$ [20]	$NaHCO_3$ [100]	C_6H_5Cl	135	24	70	84
4.	$Co(OAc)_2 \cdot 4H_2O$ [20]	$NaHCO_3$ [100]	H_2O	100	24	45	53
5.	$MnCl_2 \cdot 4H_2O$ [10]	Na_2CO_3 [100]	H_2O	100	24	Trace	15
6.	PTSA [10]	Na_2CO_3 [100]	H_2O	100	24	Trace	27
7.	P_2O_5 [10]	Na_2CO_3 [100]	$C_6H_5CH_3$	110	24	Trace	20
8.	Silica Sulfuric Acid [10]	Na_2CO_3 [100]	H_2O	100	24	20	29
9.	CAN [10]	Na_2CO_3 [100]	H_2O	100	24	–	–
10.	$CeCl_3 \cdot 7H_2O$ [10]	Na_2CO_3 [100]	H_2O	100	24	–	–
11.	$CdCl_2$ [10]	Na_2CO_3 [100]	H_2O	100	24	Trace	20
12.	$GaCl_3$ [10]	Na_2CO_3 [100]	$C_6H_5CH_3$	110	24	20	32
13.	$LiClO_4$ [10]	Na_2CO_3 [100]	H_2O	100	24	18	25
14.	$Sc(OTf)_3$ [5]	Na_2CO_3 [100]	H_2O	100	24	79	85

15.	$Sc(OTf)_3$ [10]	Na_2CO_3 [100]	H_2O	100	18	92	94
16.	$Sc(OTf)_3$ [20]	Na_2CO_3 [100]	H_2O	100	18	90	94
17.	$Sc(OTf)_3$ [10]	Na_2CO_3 [100]	$C_6H_5CH_3$	100	24	60	69
18.	$Sc(OTf)_3$ [10]	Na_2CO_3 [100]	C_6H_5Cl	135	24	63	73
19.	$Sc(OTf)_3$ [10]	$NaHCO_3$ [100]	H_2O	100	24	68	81
20.	$Sc(OTf)_3$ [10]	K_2CO_3 [100]	H_2O	100	24	51	70
21.	$Sc(OTf)_3$ [10]	DABCO [100]	H_2O	100	24	65	78
22.	$Sc(OTf)_3$ [10]	*L*–Proline [100]	H_2O	100	24	55	62

A The reactions carried out using benzaldehyde (1a) and hydroxylamine hydrochloride (2) were carried out under standard circumstances for 30 minutes at 135 °C using MW (300 W). ^{b}Yield from column chromatography in isolation.

Under reflux or MW conditions, none of the other catalytic systems tested, including CAN/Na2CO3 and CeCl3·7H2O/Na2CO3, enhanced the reaction (Table 1, entries 9, 10). Under reflux conditions, a little amount of the intended product was detected with MnCl2·4H2O/Na2CO3, PTSA/Na2CO3, P2O5/Na2CO3, and CdCl2/Na2CO3. Under MW conditions, there was a modest increase in the product yield (entry 5, 6, 7, 11). Additionally, under conventional circumstances, the yields of silica sulfuric acid/Na2CO3, GaCl3/Na2CO3, and LiClO4/Na2CO3 were poor, with only a little improvement under MW (entry 8, 12, 13). Using 10 mol% Sc(OTf)3 with 100 mol% Na2CO3 as a catalyst in water resulted in an impressively high product yield of 92% under reflux conditions (18 h) and 94% under controlled microwave irradiation (300 W, 135 °C, 30 min)—a result that caught us completely off guard (entry 15). It should be noted that Sc(OTf)3 exhibits remarkable resistance to water. Changing the catalyst molar concentration, using alternative solvents and bases, and running the reaction under various conventional and MW conditions did not result in a higher product yield.

A Reactions carried out in water with 10 mol% Sr, 1 equiv Na2CO3, and reflux conditions at 100 °C and 135 °C, respectively, under the influence of 300 W of microwave power.

B Separate yield obtained from the crude product by column chromatography.

lays forth a possible process for the creation of product 3a based on product isolation and available literature.

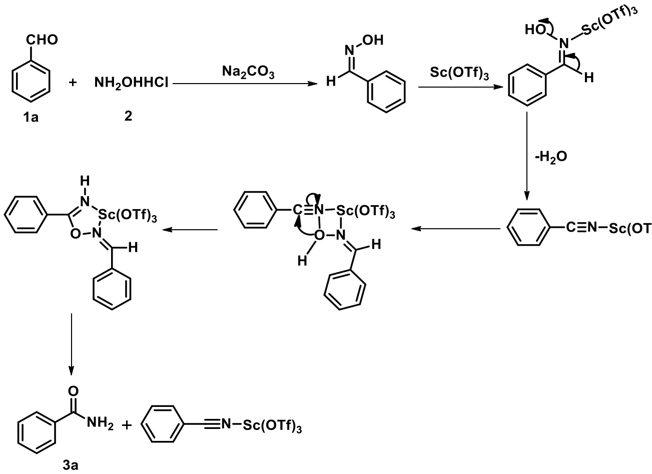
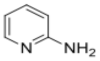
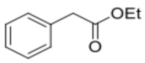
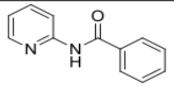
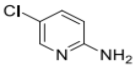
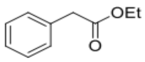
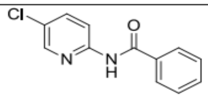
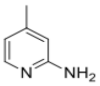
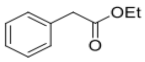
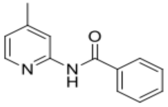
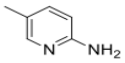
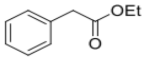
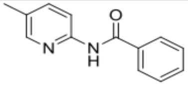
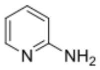
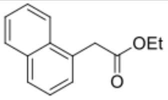
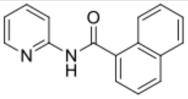
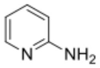
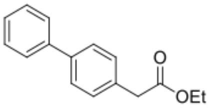
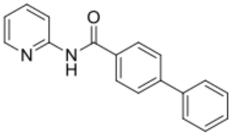
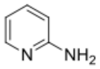
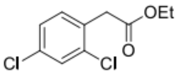
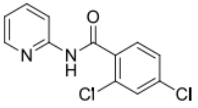
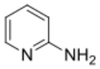
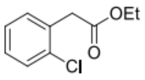
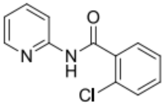
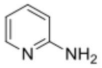
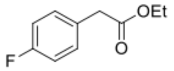
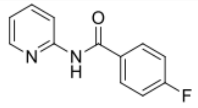
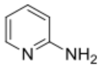
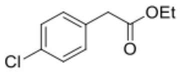
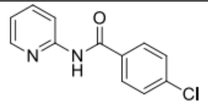
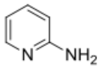
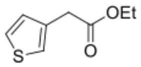
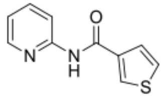
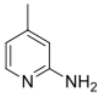
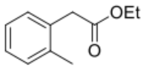
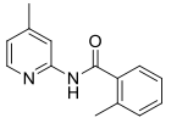
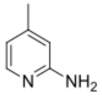
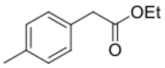
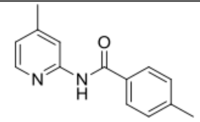
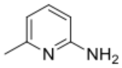
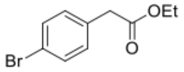
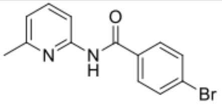
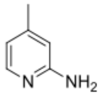
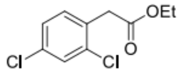
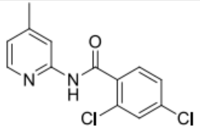
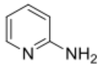
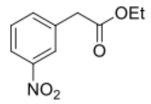
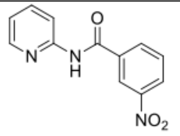


Figure:2 Plausible mechanism for the synthesis of 3a

Table 2 The scope of the reaction using 1 and 2 under optimum conditions. A

Entry	Aminopyridine (**1**)	Ethyl arylacetate (**2**)	Product (**3**)	Yield (%)^b
1	 **1a**	 **2a**	 **3a**	71
2	 **1b**	 **2a**	 **3b**	56
3	 **1c**	 **2a**	 **3c**	67
4	 **1d**	 **2a**	 **3d**	72
5	 **1a**	 **2b**	 **3e**	61
6	 **1a**	 **2c**	 **3f**	60
7	 **1a**	 **2d**	 **3g**	65
8	 **1a**	 **2e**	 **3h**	67

9	 **1a**	 **2f**	 **3i**	66
10	 **1a**	 **2g**	 **3j**	64
11	 **1a**	 **2h**	 **3k**	60
12	 **1c**	 **2i**	 **3l**	70
13	 **1c**	 **2j**	 **3m**	72
14	 **1e**	 **2k**	 **3n**	65
15	 **1c**	 **2d**	 **3o**	59
16	 **1a**	 **2l**	 **3p**	21

[a] Setup for the reaction: 1 (1.0 mmol), 2 (1.0 mmol), 20 mol% CuI, 2.0 equiv K2CO3, 1.0 mL CH3CN, 15W white CFL, 36 hours in the open air at ambient temperature. (b) Product yield isolated after column chromatography.

A few control tests were conducted to get a better understanding of the response mechanism The reaction was studied in a nitrogen environment to verify the critical function of aerobic conditions; nevertheless, the product yield was reduced by 14%, equation (a), the presence of radical scavengers such as TEMPO or BHT in the standard reaction completely inhibited the product's production. Schema 3.2.1, equation (b) shows that this 2-phenyl-N-pyridin-2-yl-acetamide cannot serve as an intermediate because its own reaction under the specified circumstances did not produce the expected product 3a. The intended product was produced in 54% yield when 1a was reacting with ethyl oxophenylacetate, suggesting that it may be an intermediate.

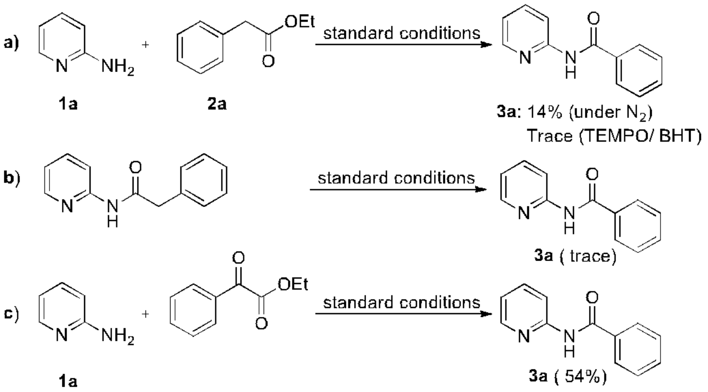


Figure:3 Control experiments.

A possible process that is supported by control trials, previous research, and product separation. When 2a is exposed to radiation when CuI is present, it produces an active intermediate I. When oxygen is added, the intermediate undergoes a series of transformations, first to hydroperoxo species (III) and then to II. Elimination of species III yields ethyl oxophenylacetate (IV). The imine V is formed when IV reacts with 1a in the presence of a base. Species VI is then generated by a further reaction between V and copper under aerobic circumstances. Species VII, VIII, and IX are sequentially used to provide the target product 3a by H abstraction from 2a, cyclization by eliminating OEt, and O-O bond cleavage with CO2 removal, respectively.

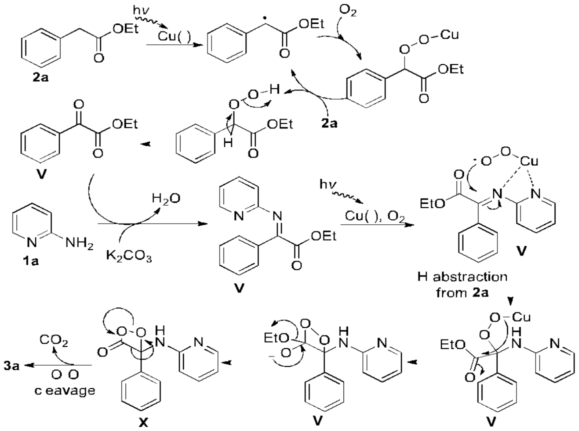


Figure: 4 Plausible mechanisms.

Our results show that 2-aminopyridines and ethyl arylacetates may be efficiently amidated aerobically under visible light at room temperature using Cu(I) as a catalyst. Effortlessly producing N-(pyridin-2-yl) benzamides, the process begins with the benzylic CH2 oxidation of ethyl arylacetates, followed by the synthesis of imines and oxidative decarbethoxylation.

Keeping all of that in mind, and as part of our continuing research,47–49, we provide here a multicomponent synthesis of 2H-indazolo[2,1-b] phthalazinetrione derivatives using a variety of aldehydes 1, dimedone 2, and phthalhydrazide 3 that is very efficient.

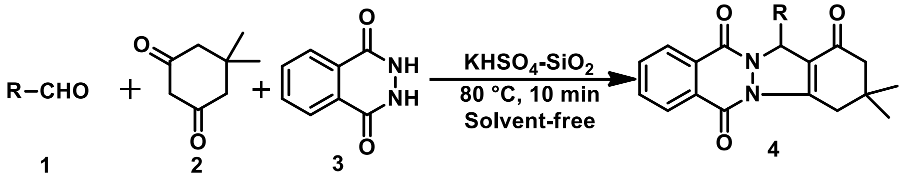


Figure:5 Synthesis of 2*H*-indazolo[2,1-*b*] phthalazine-1,6,11(13*H*)-triones.

Conclusion

There has been a recent shift in organic synthesis toward methods that are less harmful to the economy and the environment. In order to build the molecular structures, we want by connecting various organic species, new techniques have emerged as an indispensable tool, complementing more conventional ways. When it comes to pharmaceutical components in particular, air-and moisture-sensitive organometallic species might be problematic due to their inherent contamination, functional group compatibility issues, and stringent reaction conditions. Thus, under realistic reaction circumstances, modern organic chemists urgently need safer, greener, and more economically feasible alternatives. From this vantage point, research into the production of coupling products by C-H activation/functionalization based on transition metals is an extremely challenging field. employs a method that is both feasible and ecologically friendly for the sp3 C-H functionalization of α-and Y-alkyl azaarenes in aqueous medium under regulated MW using a simple organocatalyst that is compatible with water. Good to outstanding yields of physiologically relevant azaarene-substituted 3-hydroxy-2-oxindoles may be achieved quickly and mildly using this approach.

References

1. Niwadange, Sandeep. (2016). Green Chemistry Alternatives for Sustainable Development in Organic Synthesis. International Advanced Research Journal in Science, Engineering and Technology. 03. 113-115.10.17148/IARJSET.2016.3 621.
2. Woodley, John. (2019). New Frontiers in Biocatalysis for Sustainable Synthesis. Current Opinion in Green and Sustainable Chemistry. 21.10.1016/j. cogsc.2019.08.006.
3. Rai, Gopal kumar & Sri Venkatesh, Uriti & Umar, Syed & Faizuddin, Syed & Rana, Kanishka & Bhardwaj, Priya & Samanta, Debjit & Vaishnov, Ravi & Pathak, Vishal. (2024). Green Chemistry In Pharmaceutical Synthesis: Sustainable Approaches For Drug Manufacturing. World Journal of Pharmaceutical Research. 13. 389-422. 10.20959/wjpr2 0247-31865.
4. Woodley, J. M. (2019). New Frontiers in Biocatalysis for Sustainable Synthesis. Current Opinion in Green and Sustainable Chemistry, 21, 22-26.
5. Sethi, Madhuresh & Chakraborty, Palash & Shukla, R.. (2018). CHAPTER 2: Biocatalysis - A Greener Alternative in Synthetic Chemistry. 10.1039/9781782 629993-00044.
6. Divya Dhawal Bhandari et.al "Green Solvents: An Approach Towards Sustainable Development" Green Solvents: An Approach Towards Sustainable Development Volume 3, Book 19, Part 1, Chapter 1
7. Nguyen Thanh Quang et.al "Development of A Decision Support System For Companies In The Energy From Biomass Area, Applying Circular Economy Principles With A Life Cycle Thinking Approach"2023

8. Kate, Aditya & Sahu, Lavanya & Pandey, Jaya & Mishra, Mohit & Sharma, Prasanna. (2021). Green catalysis for chemical transformation: The need for the sustainable development. Current Research in Green and Sustainable Chemistry. 5. 100248. 10.1016/j.crgsc.2021.100248.
9. Nasrollahzadeh, Mahmoud & Sajjadi, Mohaddeseh. (2021). An introduction to green chemistry. 10.1016/B978-0-12-822108-2.00001-6.
10. Majhi, Sasadhar. (2023). Applications of Flow Chemistry in Total Synthesis of Natural Products. Current Organic Chemistry. 27. 1072-1089. 10.2174/1385272827666230809094232.
11. Basavanna, Vrushabendra & Puttappa, Sneha & Chandramouli, Manasa & Ningaiah, Srikant Murthy. (2023). Green Synthetic Methods for the Cycloaddition Reactions: A Mini Review. Polycyclic Aromatic Compounds. 43. 1-22. 10.1080/10406638.2022.2162933.
12. Vaccaro, Luigi. (2020). Green Shades in Organic Synthesis. European Journal of Organic Chemistry. 2020. 10.1002/ejoc.202000131.
13. Mulvihill, Martin & Beach, Evan & Zimmerman, Julie & Anastas, Paul. (2011). Green Chemistry and Green Engineering: A Framework for Sustainable Technology Development. Annual Review of Environment and Resources. 36. 271-293. 10.1146/annurev-environ-032009-095500.
14. Rossino, Giacomo & Robescu, Marina & Licastro, Ester & Tedesco, Claudia & Martello, Ilaria & Maffei, Luciana & Vincenti, Gregory & Bavaro, Teodora & Collina, Simona. (2022). Biocatalysis: A smart and green tool for the preparation of chiral drugs. Chirality. 34. 10.1002/chir.23498.