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Review

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Advances in sustainable synthesis: the role of green solvents and biocatalysts

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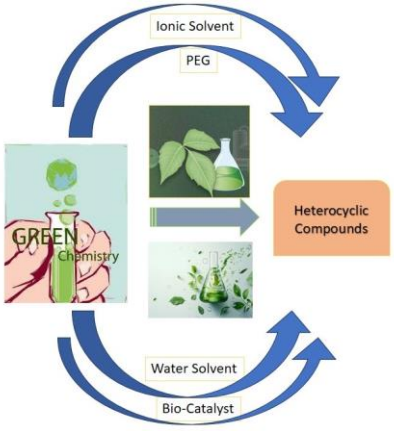
Abstract

One of the most promising concepts in sustainable chemistry is “Green Chemistry”. This approach focuses on innovations in chemical investigation and production that minimize or eliminate the use of poisonous, dangerous, and bio-accumulative materials in the design, manufacture, and application in chemical production. Various strategies within Green Chemistry, like usage of green solvents, transformations, and biocatalysts, are discussed in detail in this review. These methods enable synthetic chemists to work under mild conditions, using environmentally friendly procedures, alternative feedstocks, and energy-efficient processes. They also help reduce the formation of by-products and waste, improve reproducibility, and increase product yields. By addressing the limitations of traditional synthesis methods such as harmful solvents, slow reaction rates, and lengthy reaction times - Green Chemistry thus offers a more sustainable and efficient approach.



Keywords: Green chemistry, sustainable chemistry, ionic liquids, biocatalysts, synthesis, transformations

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1. Introduction

The Twelve Principles of Green Chemistry[1], emphasize key strategies for making chemical processes safer and more sustainable. These principles include prevention of waste, atom economy, safer chemical synthesis, the design of safer chemicals and solvents, energy saving, the utilization of biomass, reduction of unnecessary derivatization, catalysis, deterioration, source reduction, and safer chemistry practices to minimize accidents. Together, they provide a framework for reducing the environmental impact of chemical production.

A primary goal in modern synthetic chemistry is to avoid risky solvents in chemical processes and replace them with more environmentally friendly alternatives. Traditional solvents widely used in chemical, pharmaceutical, biomedical, and separation processes pose a major challenge to Green Chemistry because of their inherent toxicity, volatility, and flammability. Volatile organic compounds (VOCs), such as dimethylformamide (DMF) and chloroform ($CHCl_3$) are widely used but pose serious environmental and healthiness hazards. Chloroform, for example, can give to ozone depletion as well as global warming when it is converted into chlorofluorocarbons (CFCs). Other solvents, like DMF and dimethyl sulfoxide (DMSO), are problematic because of their water miscibility, which leads to the contamination of water sources.

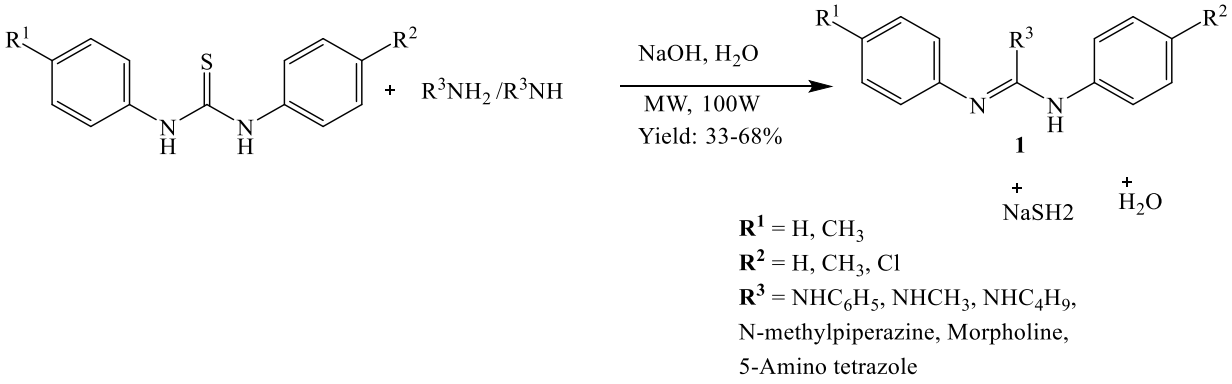
Since the introduction of Twelve Principles of Green Chemistry, significant efforts have been made to replace traditional solvents with environmentally friendly alternatives. Among these, water has become the most widely adopted green solvent, followed by ionic liquids, surfactants, supercritical fluids, fluorous solvents, liquid polymers, bio-based solvents, and switchable solvent systems. These alternatives reduce environmental risks and contribute to safer, more sustainable chemical practices. While doing literature survey, the authors came across a number of review articles on green solvents and sustainability[2-4]. However, an article by Clarke et al.[5] provides a comprehensive and systematic overview of green and sustainable solvents used in chemical processes, emphasizing their environmental impact, performance, and industrial applicability. The review extensively covers various classes of green solvents, including water, ionic liquids (ILs), deep eutectic solvents (DESs), supercritical fluids (notably CO_2), and bio-based solvents like 2-methyltetrahydrofuran and ethyl lactate. The article also highlights how these solvents are applied across different chemical transformations, such as organic synthesis, catalysis, separations, and biocatalysis, often enabling improved efficiency, selectivity, or waste reduction. Furthermore, the review addresses regulatory frameworks and industrial considerations, noting challenges such as cost, scalability, and solvent recovery. Modivated by these studies and keeping in view the importance of green and sustainable solvents, we tried our best to write a review on recent advances on sustainable synthesis. This present review offers a broad summary of the usage of green solvents i.e. water, ionic liquids, PEG and biocatalysts and their importance in advancing the goals of Green Chemistry.

2. Literature Review

2.1. Water as a green solvent

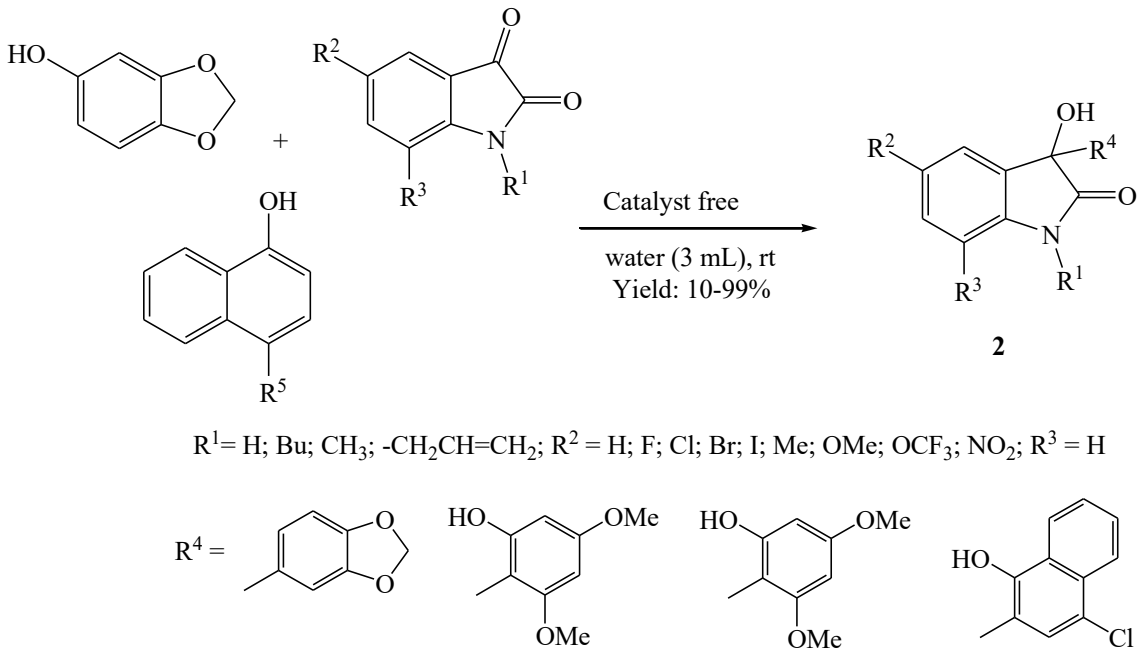
Water is often called the "solvent of life" due to its critical role in sustaining all known living organisms. It is considered indispensable for life as we know it and may also be essential for any undiscovered life forms that might exist elsewhere in the universe[6]. Within living organisms, water serves as a highly effective solvent, supporting a wide range of critical physiological functions. For example, it dissolves numerous types of molecules, participates in essential metabolic pathways, and helps maintain acid-base balance while facilitating enzyme activity. These beneficial properties also make water an invaluable solvent in the laboratory for chemists. In addition to its usefulness, Water is widely regarded by researchers as the greenest solvent in chemistry, both for experimental applications and industrial processes[7-8]. Ideally, the most optimal scenario is a solvent-free reaction; however, when a solvent is required, water is often the preferred choice. The usage of water in compound synthesis is one of the most extensively studied approaches in green chemistry[9-11]. Water offers several advantages as a solvent, including its strong hydrogen bonding capability, high specific heat capacity, elevated dielectric constant, significant surface tension, and low viscosity. Water's remarkable characteristics such as being ecofriendly, incombustible, abundant, inexpensive, and having the ability to interact with microwaves and act as an energy transfer medium-make it highly suitable for safe and effective organic synthesis. Thus, using aqueous medium aligns seamlessly with the current push for additional sustainable chemical industry, one that prioritizes the usage of renewable raw materials over fossil fuels as a primary resource.

Sanghvi *et al*.[12] described the production of guanidines **1** (Scheme 1) *via* reaction of thioureas with amines in alkaline conditions using water as a solvent and microwave irradiation at 100 W for 10-95 minutes. This method has numerous advantages such as reasonable yield and the effective neutralization of hazardous hydrogen sulfide (H_2S) gas by the reaction mixture.



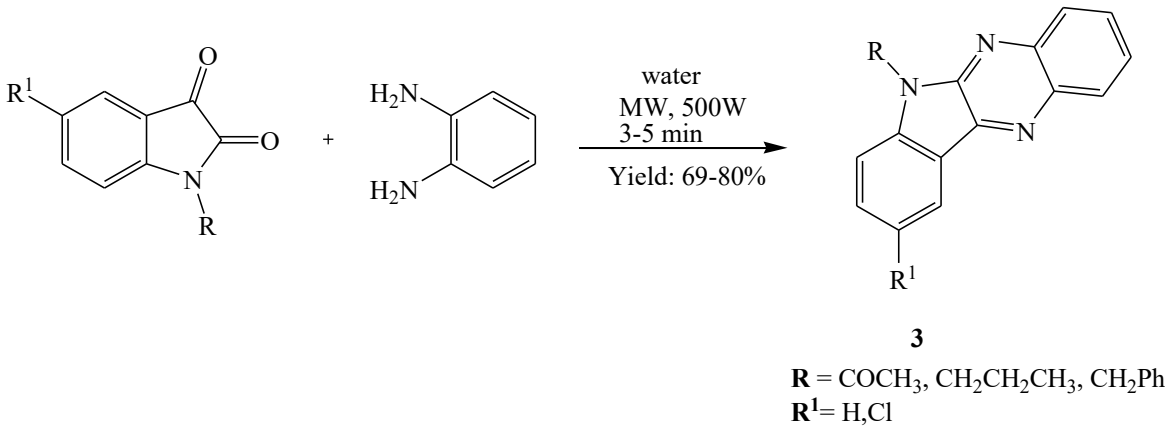
Scheme 1. Synthesis of guanidines **1**.

Kumar *et al.* reported the synthesis of 3-aryl-3-hydroxy-2-oxindoles **2** (Scheme 2) using water[13]. The study highlights water's advantages as a sustainable reaction medium owing to its safety, affordability and environmental friendliness. The reaction involves isatin and phenol derivatives, where water acts as a catalyst through hydrogen-bonding interactions, facilitating the reaction without requiring conventional catalysts. The study further demonstrated the broad substrate scope, successfully reacting various substituted isatins and phenols to afford bioactive 3-hydroxy-2-oxindole derivatives **2**. This work represents an eco-friendly and efficient route for synthesizing compounds with significant biological activity.



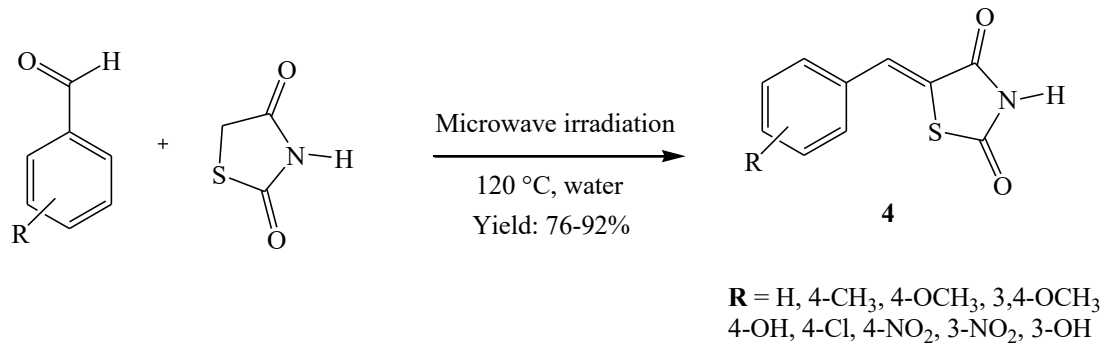
Scheme 2. Synthesis of 3-aryl-3-hydroxy-2-oxindoles **2**.

A water mediated synthesis of quinoxalines **3** (Scheme 3) *via* condensation of isatins and o-phenylenediamine was reported by Bajpai *et al*[14]. This approach is gentle, affordable, eco-friendly, and remarkably efficient, producing the product **3** in consistently high yields.



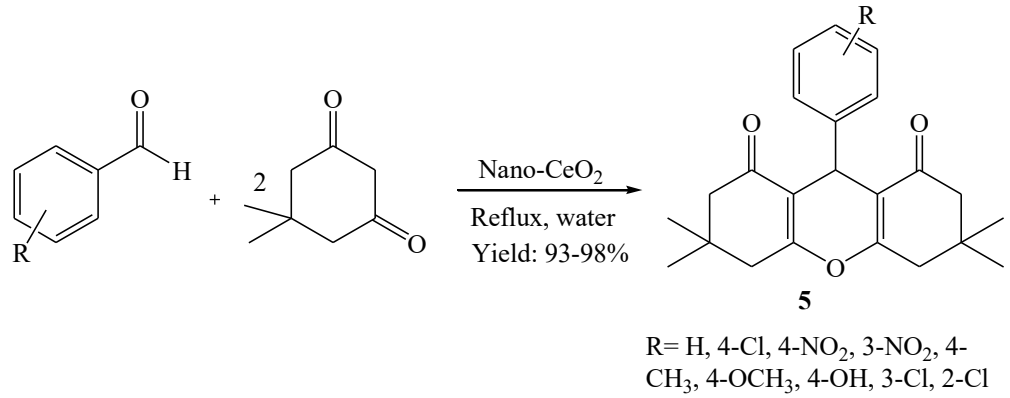
Scheme 3. Synthesis of quinoxalines **3**.

A method for synthesizing benzylidenethiazolidine-2,4-diones **4** (Scheme 4) through a reaction of aromatic aldehydes and thiazolidine-2,4-dione was described by Bhat *et al.*[15]. The process employed microwave irradiation at 250 W at 120 ˚C for 2-5 minutes in aqueous medium. In this protocol, various solvents, including ethanol, DMF, and DMSO, were tested; however, water proved the most effective. This protocol has numerous benefits, including greater yields, smaller reaction times, and environmental friendliness.



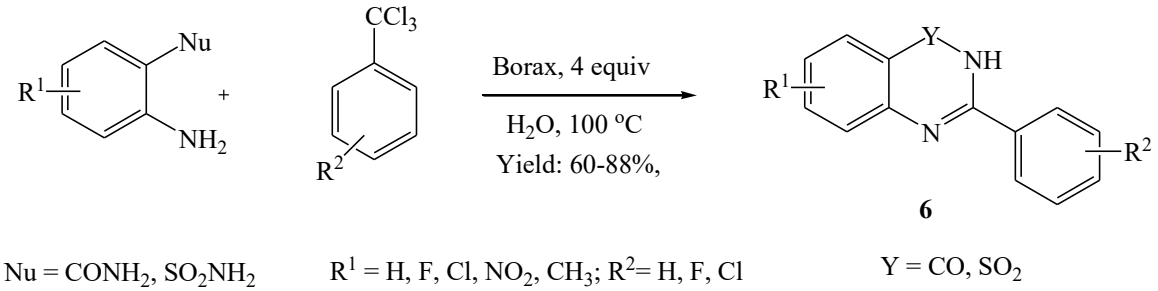
Scheme 4. Synthesis of benzylidenethiazolidine-2,4-diones **4**.

Synthesis of 1,8-dioxooctahydroxanthenes **5** (Scheme 5) through the reaction of aromatic aldehydes and dimedones, catalyzed by nano-CeO_2 in refluxing water for 1 h was reported by Baghernejad and Ghapanvari[16]. This protocol has advantages of high efficiency and the ease of catalyst recovery.

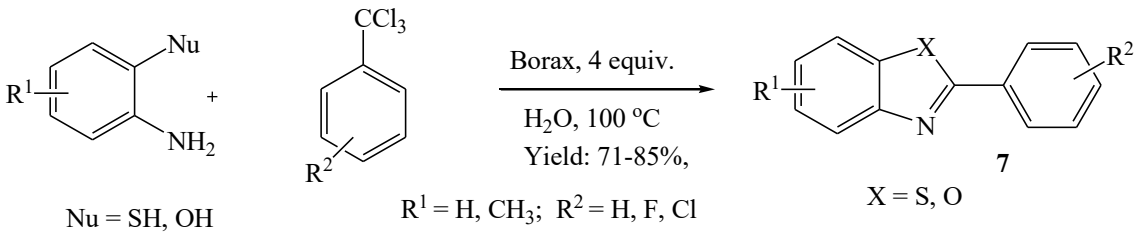


Scheme 5. Synthesis of 1,8-dioxooctahydroxanthenes **5**.

Rao and Hussain[17] reported the formation of quinazolin-4(3*H*)-one/benzothiadiazine 1,1-dioxides **6** (Scheme 6) by reacting 2-Aminobenzamide/2-aminobenzenesulfonamide with α, α, α-trichlorotoluene and borax in H_2O at 100 °C. They have also reported the synthesis of benzothiazole/benzoxazoles **7** (Scheme 7) *via* reacting 2-aminothiophenol/2-aminophenol with α, α, α-trichlorotoluene using borax in H_2O at 100 °C.

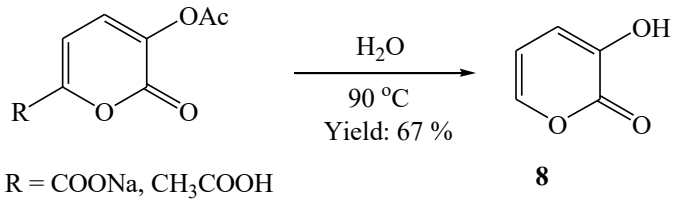


Scheme 6. Synthesis of quinazolin-4(3*H*)-one/benzothiadiazine 1,1-dioxides **6**.



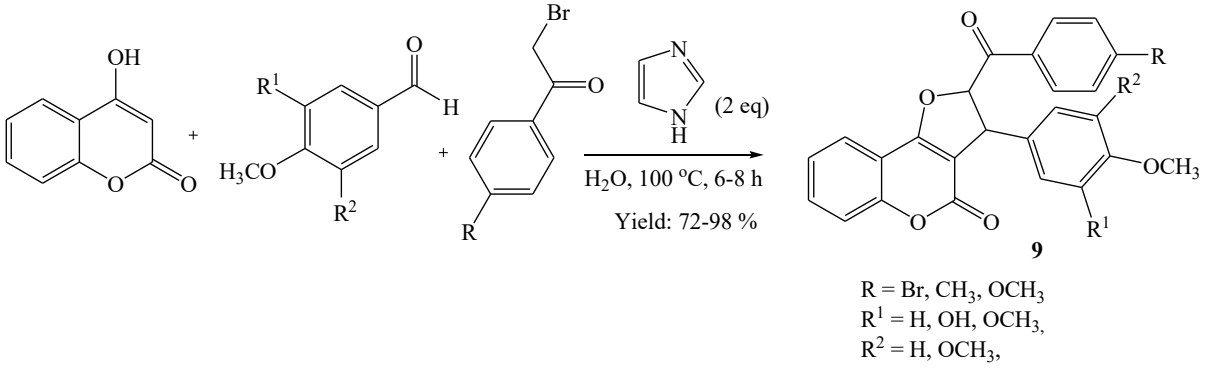
Scheme 7. Synthesis of benzothiazole/benzoxazoles **7**.

Leonardi *et al* described the formation of 3-Hydroxy-2-pyrone **8** (Scheme 8) by simply heating 6-caboxylic-3-hydroxy-2-pyrones in water at 90 °C[18].



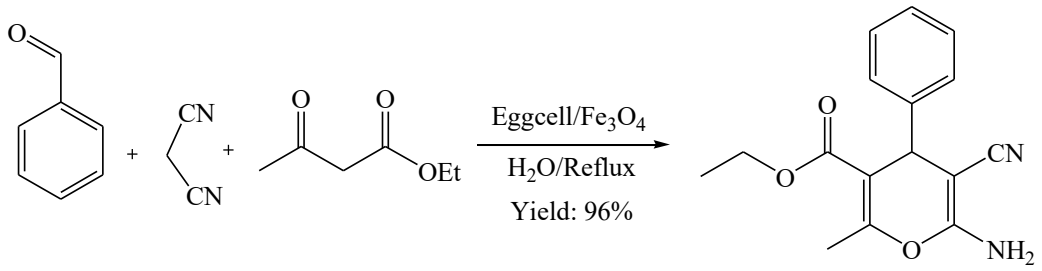
Scheme 8. Synthesis of 3-Hydroxy-2-pyrone **8**.

Mali *et al.* have described multicomponent synthesis of *trans*-2,3-dihydrofuro[3,2-c]coumarins **9** (Scheme 9). This method involves the reaction of 4-hydroxycoumarin, 2-bromoacetophenones, and aldehydes, using an imidazole catalyst with water as the solvent[19].



Scheme 9. Synthesis of *trans*-2,3-dihydrofuro[3,2-c]coumarins **9**.

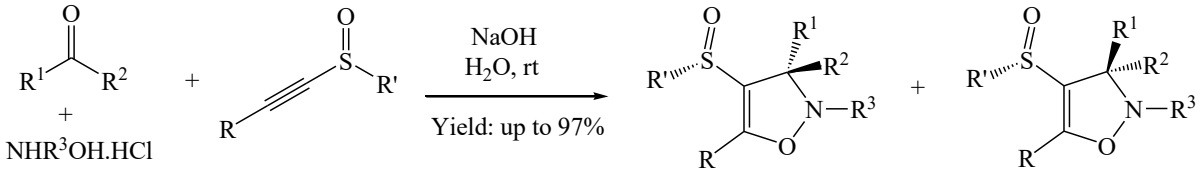
Ghafuri *et al* have reported the synthesis of the 2-amino-3-cyano-(4*H*)-chromenes **10** (Scheme 10) by multicomponent reaction of benzaldehyde, malononitrile, and ethyl acetoacetate using Eggshell/Fe_3O_4 catalyst in refluxing water for 10 min[20]. The advantage of this method is biodegradable catalyst with easy recovery as well as reusability and short reaction time.



10

Scheme 10. Synthesis of the 2-amino-3-cyano-(4*H*)-chromenes **10**.

Liao *et al.* have described two eco-friendly, efficient protocols for synthesizing (polyfluoro)alkanesulfinyl 4-isoxazolines **11a and 11b** (Scheme 11)[21]. The key reaction is a [3+2] cycloaddition between nitrones and α-alkynyl sulfoxides under catalyst- and solvent-free conditions. The method shows high tolerance for various functional groups on both the nitrone and sulfoxide components, yielding polyfluoroalkyl or alkyl sulfinyl 4-isoxazolines in excellent yields. A significant contribution of this work is its focus on green chemistry principles. The authors advanced their methodology by developing a one-pot synthesis in water as solvent, eliminating the need to isolate nitrones and thereby enhancing overall efficiency. The authors further developed a one-pot synthesis in an aqueous medium without isolation of nitrones, thus improving efficiency. This one-pot process, using aldehydes, hydroxylamine hydrochlorides, and sulfoxides in water, provides comparable or better yields than the solvent-free method for many substrates. This approach highlights both the synthetic utility of the process and its environmental advantages, emphasizing the use of minimal solvents and avoiding catalysts, aligning with green chemistry's goals of reducing waste and energy consumption.

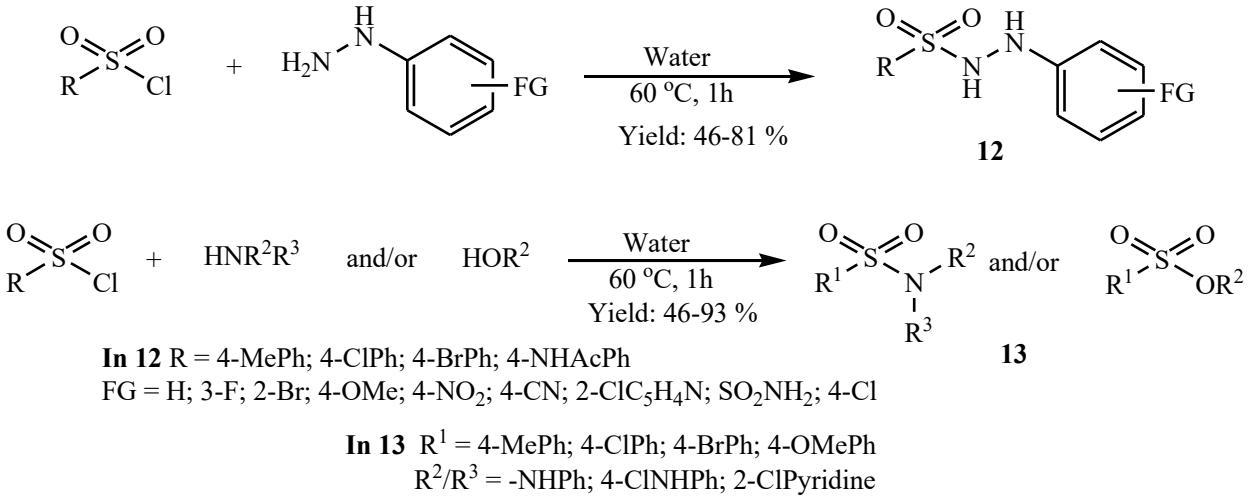


11a **11b**

R = Ph; 2-MePh; 3-MePh; 4-MePh; 4-ClPh; 4-BrPh
R^1 = 2-MePh; 3-MePh; 4-MePh; 4-OMePh; 4-ClPh; 4-BrPh; 4-CF_3Ph, Thienyl
R^2 = H and R^3 = Me; t-Bu

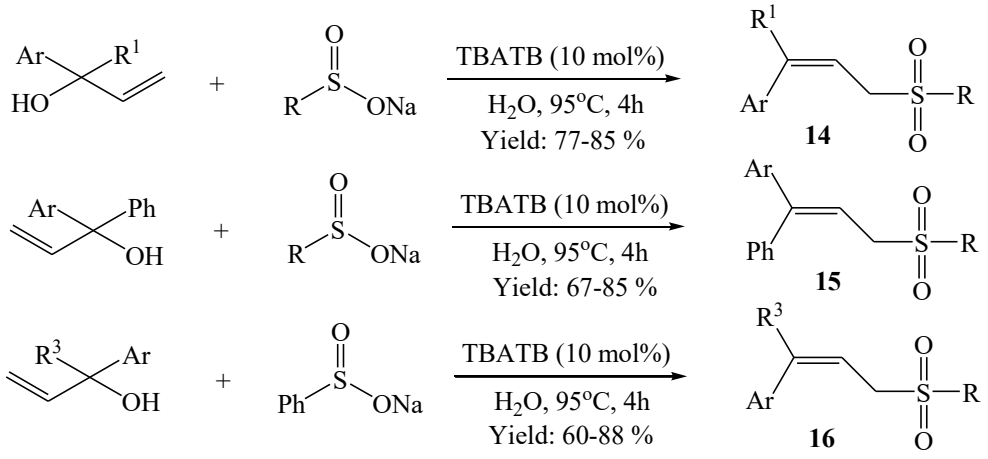
Scheme 11. Synthesis of (polyfluoro)alkanesulfinyl 4-isoxazolines **11a** and **11b**.

Noda and Tanimari reported a method involving green chemistry for synthesizing sulfonyl hydrazides **12** and **13** (Scheme 12) in water[22]. The reaction of sulfonyl chlorides and hydrazines, in the presence of triethylamine (added when hydrazines are in hydrochloride form) was conducted at 60°C for 1 h to obtain **12** and 13 The method is environmentally friendly and reduces waste, offering a sustainable alternative for synthesizing sulfonyl hydrazides.



Scheme 12. Synthesis of sulfonyl hydrazides **12** and **13**.

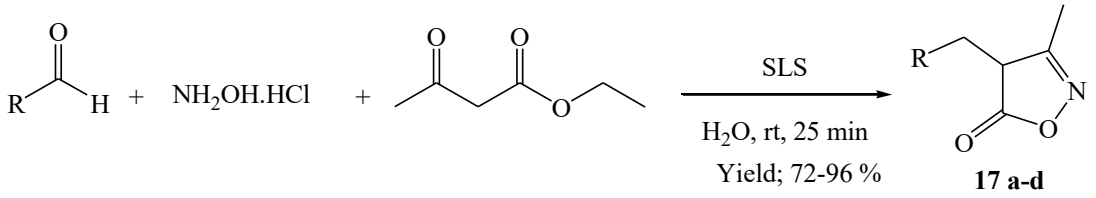
Jia *et al.* introduced a novel, one-pot method for synthesizing allyl sulfones **14**, **15** and **16** (Scheme 13) by cross-coupling allyl alcohols with sodium sulfinates in water[23]. The reaction uses tetrabutylammonium tribromide (TBATB) as a catalyst, highlighting the simplicity and environmentally friendly nature of the process. Allyl sulfones, which possess valuable biological and synthetic properties, are produced in excellent yields. The reaction occurs at 95 °C for 4 hours and favors the formation of the E isomer in asymmetric substrates. Mechanistically, the reaction is radical-mediated, with TBATB decomposing into bromine, which facilitates the formation of sulfonyl radicals from sodium sulfinates, leading to the formation of allyl sulfones. Key features of this protocol comprise the use of inexpensive reagents and the absence of toxic metals, making it an eco-friendly method.



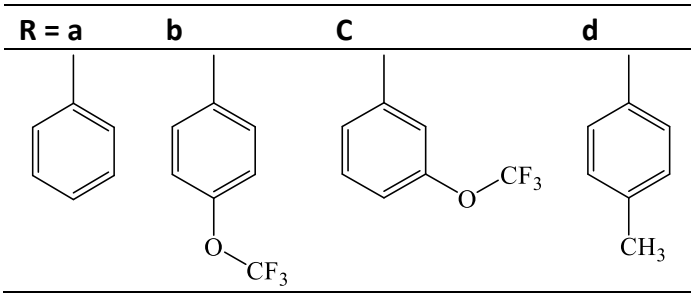
Scheme 13. Synthesis of allyl sulfones **14**, **15** and **16**.

Compound	
14	R = Ph; Me; 4-FPh; 4-ClPh; 4-MePh
	R^1 = Ph ; 4-FPh; 4-ClPh; 4-MePh; 4-BrPh; 4-OCH_3Ph
	Ar = Ph ; 4-FPh; 4-ClPh; 4-MePh; 4-BrPh; 4-OCH_3Ph
15	R = Ph
	Ar = 2-MePh; 3-MePh; 4-MePh; 2-ClPh; 3-ClPh ; 4-ClPh; 4-BrPh; Biphenyl; 4-EtPh; 2-FPh
16	R^3 = H; Me
	Ar = Thienyl; Furan; Ph; 4-FPh; 3-ClPh; 4-CF_3Ph

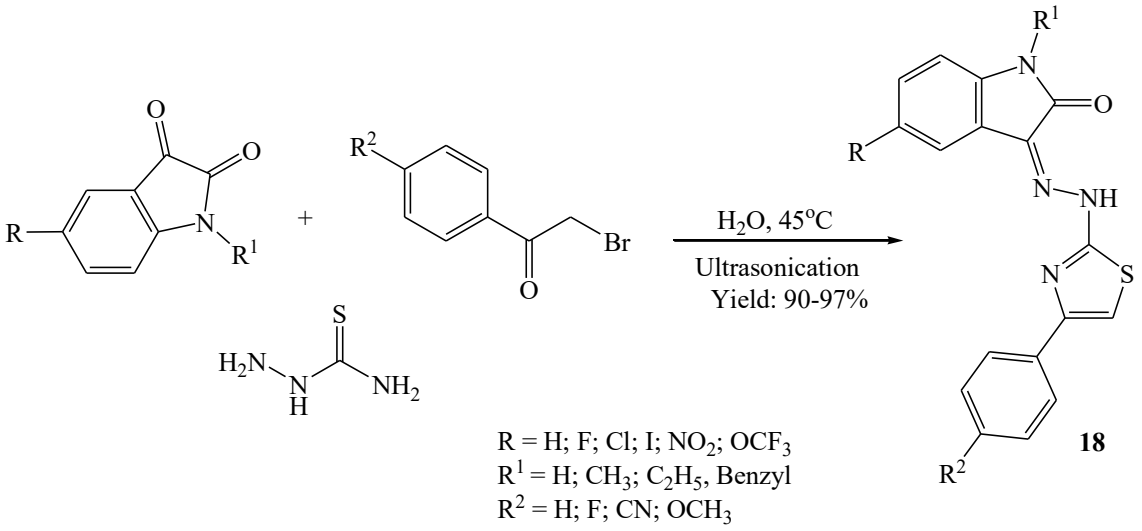
A green method for synthesizing isoxazole-5(4*H*)-ones **17** (Scheme 14) employing sodium lauryl sulfate (SLS) as a micellar catalyst using water has been reported by Bhowmik and co-workers[24]. Isoxazoles are important in pharmaceuticals, and this method avoids toxic solvents and metal catalysts. The reaction involves benzaldehyde, ethyl acetoacetate and hydroxylamine hydrochloride with SLS creating micelles that enhance the reaction by increasing the interaction of hydrophobic reactants. The process achieves a high yield (97%) under mild conditions, with the catalyst being recyclable up to four times. The method is eco-friendly, efficient, and eliminates the need for chromatographic purification.



Scheme 14. Synthesis of isoxazole-5(4*H*)-ones **17**.



Khanum and co-workers outlined a method for the production of novel hydrazino thiazoles **18** (Scheme 15) *via* a single-step multicomponent reaction of isatins, arylacyl bromides and hydrazinecarbothioamide in water under ultrasonication[25]. The methodology is notable for its green chemistry approach, yielding high efficiency and significant functional group tolerance without the need for chromatographic purification. The reaction conditions were optimized, revealing that sonication at 45°C leads to a 97% yield within 30-35 minutes. The synthesized compounds exhibited promising antioxidant activity, with IC_{50} values indicating strong efficacy. Additionally, in-silico ADME studies suggested the potential for these compounds to serve as oral and intravenous therapeutic agents. This research highlights the effective utilization of water as a solvent and the advantages of ultrasonication in developing biologically active heterocyclic compounds, contributing valuable insights into sustainable synthetic methodologies in medicinal chemistry.



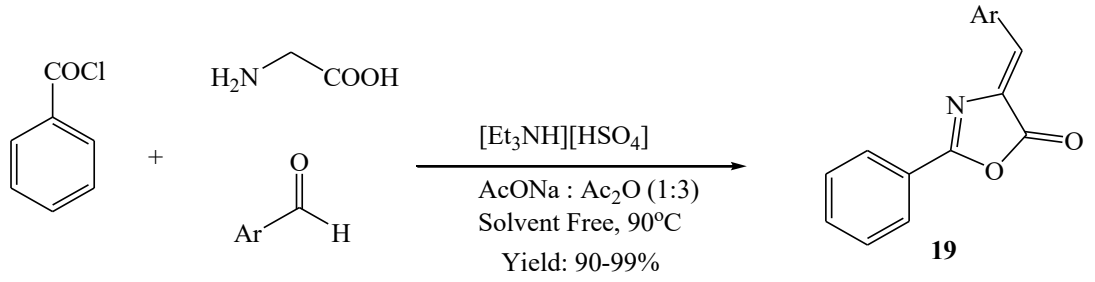
Scheme 15. Synthesis of hydrazino thiazoles **18**.

2.2. Ionic liquids (ILs) as green solvents

Ionic liquids (ILs) are a distinctive group of low-melting, semi-organic salts or salt blends with diverse and expanding applications. They are typically composed of organic cations and anions, which contribute to their distinct properties, such as low viscosity and remarkable versatility. One of the most significant advantages of ILs is their environmental friendliness, as they offer a sustainable substitute to volatile organic solvents because of their extremely low vapor pressures. Additionally, ILs often function as catalysts, further enhancing their utility in green chemistry.

These liquids are highly prized for their exceptional chemical and thermal stability, non-flammability, excellent ionic conductivity, and wide electrochemical stability range. Such characteristics make them ideal for various applications, including their use as solvents and reagents in chemical reactions. Moreover, ILs have found applications in separation processes, polymerization techniques, electrochemical systems, and enzymatic processes. Their adaptability across these fields highlights their potential to revolutionize conventional methodologies in both industrial and laboratory settings.

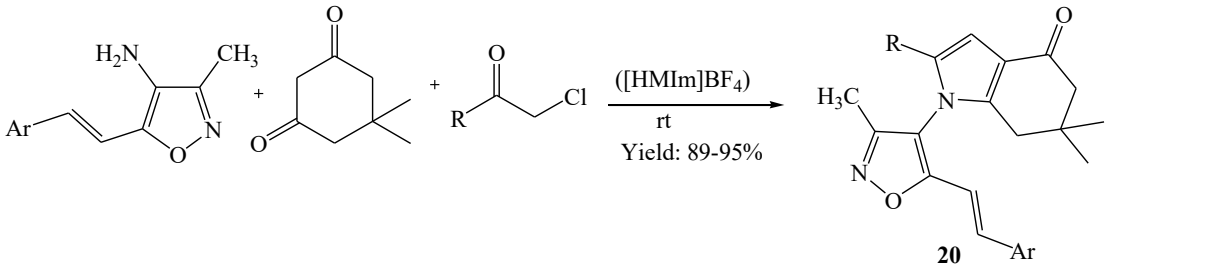
An eco-friendly, solvent-free method for synthesizing 4-arylidene-2-phenyl-5(4*H*)-oxazolones **19** (Scheme 16)**,** catalyzed by the ionic liquid [Et_3NH][HSO_4], was described by Jadhav and co-workers[26]. The multicomponent reaction combines benzoyl chloride, glycine, and aromatic aldehydes, producing high yields (90-99%) in just 20-25 minutes at 90°C. The process is green, as it avoids toxic solvents and allows catalyst reuse. The prepared oxazolones were identified using FTIR, NMR, and mass spectrometry, confirming their structures. This method offers a greener alternative to traditional oxazolone synthesis, with faster reactions and better yields.



Scheme 16. Synthesis of 4-arylidene-2-phenyl-5(4*H*)-oxazolones **19**.

19	Ar	19	Ar
a	C_6H_5	j	2-ClC_6H_4
b	4-$CH_3C_6H_4$	k	2,6-$Cl_2C_6H_4$
c	4-$CH_3OC_6H_4$	l	3,4,5$(OMe)_3C_6H_3$
d	4-ClC_6H_4	m	4-$N(Me)_2C_6H_4$
e	4-BrC_6H_4	n	4-pyridine
f	4-FC_6H_4	o	2-thiophene
g	4-$NO_2C_6H_4$	p	2-furan
h	3-$NO_2C_6H_4$	q	4-benzaldehyde/benzene 4-carbaldehyde
i	2-$NO_2C_6H_4$	r	4-OH,3-OEt benzaldehyde

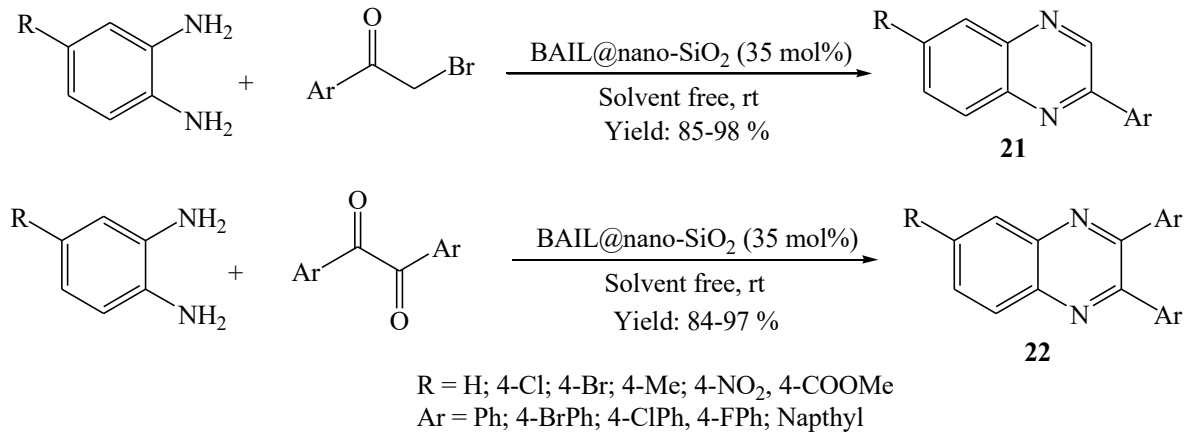
Modugu and Pittala have reported a single-step, multicomponent reaction of 4-amino-3-methyl-5-styrylisoxazoles, dimedone, and chloroacetophenones[27]. The reaction was carried out at room temperature by using the ionic liquid 1-methylimidazolium tetrafluoroborate ([HMIm]BF_4) without the need for a catalyst. This results in the production of isoxazolyl dihydro-1*H*-indol-4(5*H*)-ones **20** (Scheme 17). This method provides numerous advantages, including high product yields, simplicity of operation, mild and neutral reaction conditions, and a reduced environmental footprint.



Ar, R = C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-OHC_6H_4, 4-$NO_2C_6H_4$,

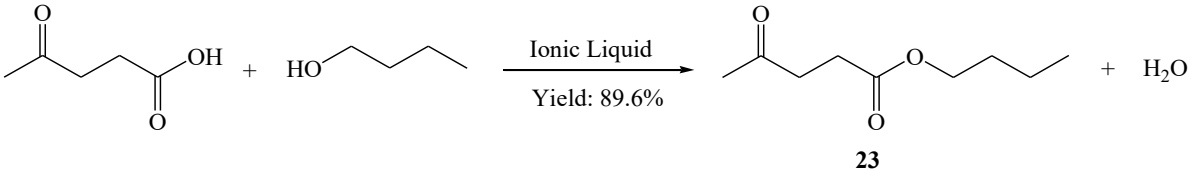
Scheme 17. Synthesis of isoxazolyl dihydro-1*H*-indol-4(5*H*)-ones **20**.

Daragahi and co-workers introduced a green method for synthesizing quinoxalines **21** and **22** (Scheme 18) using an ionic liquid (BAIL) supported on nano-SiO_2[28]. Quinoxalines were synthesized by reacting α-haloketones or benzil with 1,2-phenylenediamines. The conditions were optimized to provide effective yields (up to 98%) at normal temperature. The method also allows for efficient catalyst recovery and reuse upto six cycles. This approach offers an eco-friendly, efficient, and recyclable solution for quinoxaline synthesis.



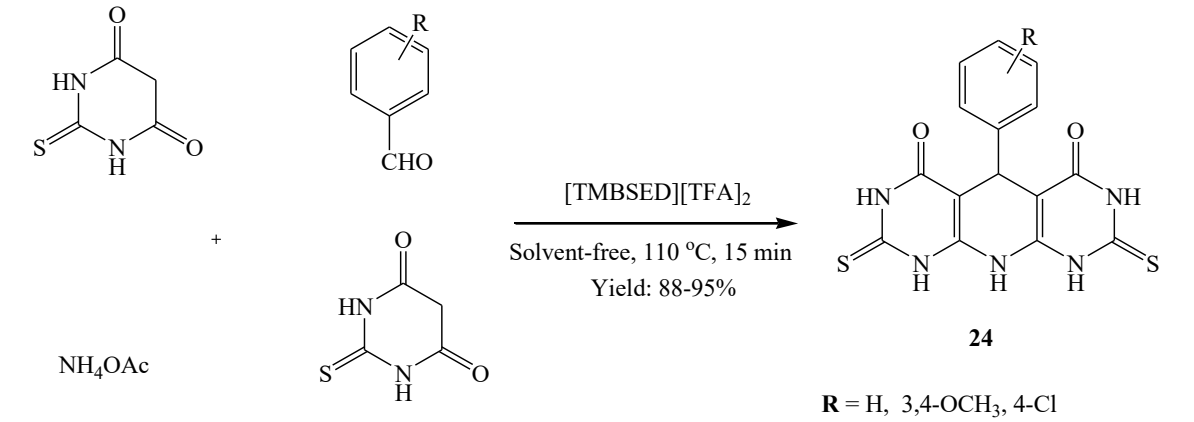
Scheme 18. Synthesis of quinoxalines **21** and **22**.

Kalghatgi *et al*[29] reported the synthesis of n-butyl levulinate **23** (Scheme 19) through the esterification of levulinic acid with n-butanol, employing the ionic liquid [MIM][HSO_4] as a catalyst in a solvent-free system. The reaction conditions were optimized using response surface methodology. The process achieved 89.6% yield and 98.1% selectivity at 90°C. The method is sustainable, offering easy product separation and applicability for synthesizing other levulinate esters.



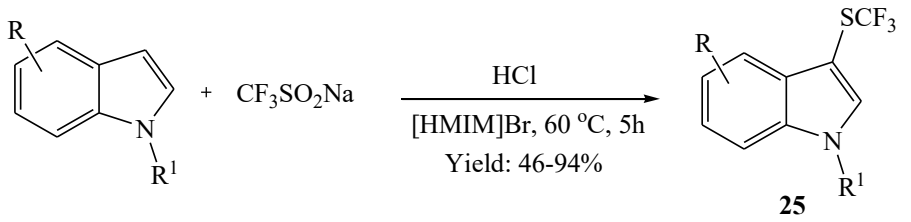
Scheme 19. Synthesis of n-butyl levulinate **23**.

Atashrooz and Zare[30] reported the production of pyrido[2,3-*d*:6:5-*d'*]dipyrimidines **24** (Scheme 20) by the reaction of aryl aldehydes, ammonium acetate, and 2-thiobarbituric acid at 110°C without using any solvent in the presence of ionic liquid, N^1,N^1,N^2,N^2-tetramethyl-N^1,N^2-bis(sulfo)ethane-1,2-diaminium trifluoroacetate ([TMBSED][$TFA]_2$) as a catalyst.



Scheme 20. Synthesis of pyrido[2,3-*d*:6:5-*d'*]dipyrimidines **24**.

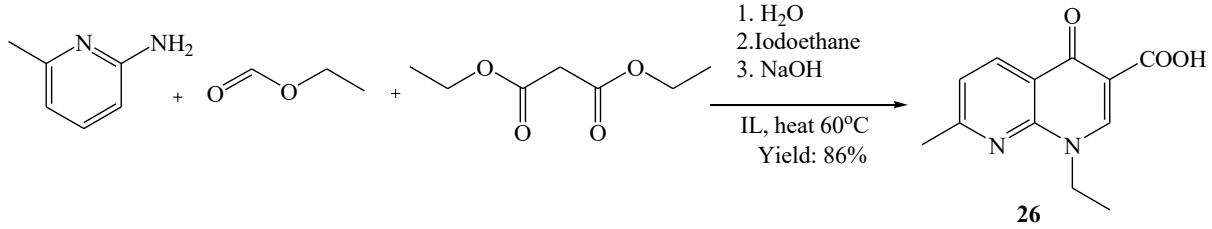
Wang and the team[31] have reported the synthesis of indoles **25** (Scheme 21) having trifluoromethylthiol groups using sodium trifluoromethanesulfinates in [HMIM]Br as an ionic liquid. The solvent not only helps to recycle the reaction mixture, but also acts as a reductant. This method has many advantages such as a simple process, employing a recyclable solvent and eliminating the need for transition metals and phosphorus and the ability to perform gram-scale synthesis.



R= H, CH_3, OCH_3, Br, Cl, F, NO_2,
R^1 = H, CH_3, CH_2CH_3

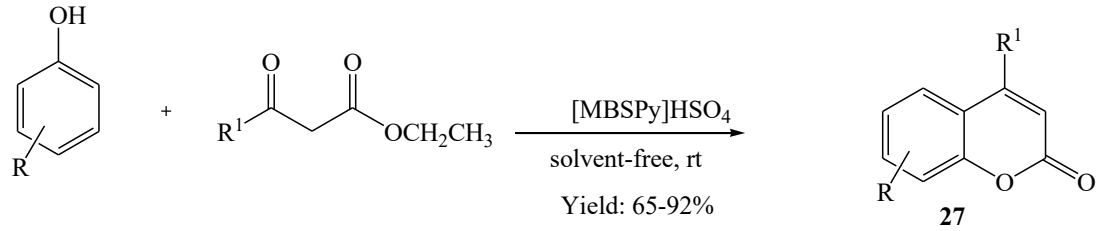
Scheme 21. Synthesis of indoles **25**.

Ahfad-Hosseini and colleagues[32] have published a report on the synthesis of Nalidixic acid **26** (Scheme 22). The acid was produced by combining 6-methylpyridin-2-amine, diethyl malonate and ethyl formate in presence of an ionic liquid called tris-(2-hydroxyethyl)ammonium acetate, aqueous ethanol, iodomethane, and sodium hydroxide at 60 °C. This method has several benefits, involving shorter reaction time, reusability of the IL and an easy isolation of the final product.



Scheme 22. Synthesis of Nalidixic acid **26**.

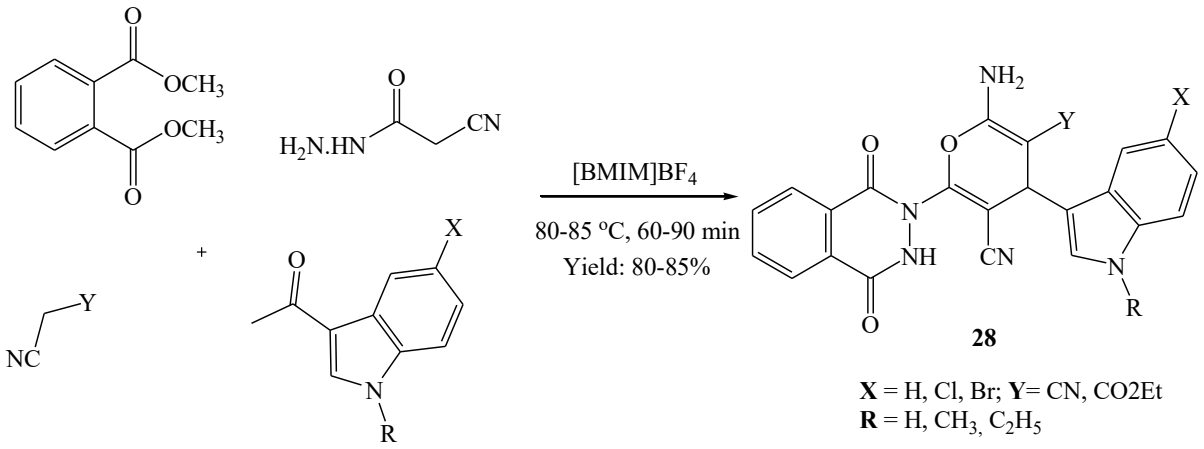
Uross *et al* synthesized several coumarin derivatives **27** (Scheme 23) through reaction of phenols and β-ketoester, catalyzed by IL, 1-butylsulfonic-3-methylpyridinium hydrogen sulfate [MBSPy][HSO_4], in solvent-free condition[33]. This protocol offers advantages like excellent product yields, rapid reaction times, straightforward catalyst recovery, and recyclability.



R= OH, OH &CH_3, di-OH,
$\mathbf{R^1}$= CH_3, CH_2Cl

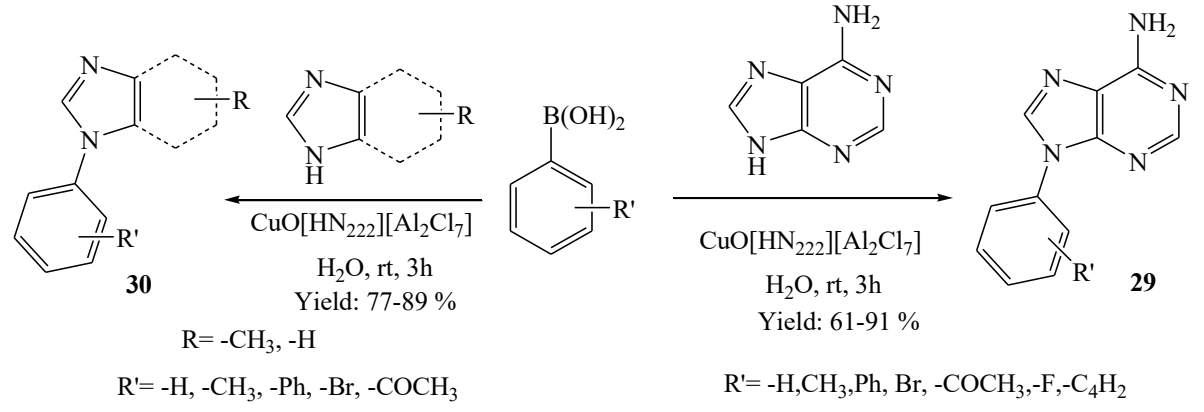
Scheme 23. Synthesis of coumarin derivatives **27**.

Malik *et al*[34] reported the synthesis of indole-pyran hybrids **28** (Scheme 24). They carried out a four-component reaction by using IL, 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM]BF_4) as a solvent. To obtain **28**, a mixture of dimethyl phthalate, cyanoacetohydrazide, 1*H*-indole-3-carbaldehydes, malononitrile/ethyl 2-cyanoacetate and [BMIM]BF_4 was heated at 80-85 °C for 1-1.5 hr. They also tested other solvents like ethanol and dimethylformamide along with water. However, the results showed that organic solvents provided a lower yield when compared to the ionic liquid [BMIM]BF_4.



Scheme 24. Synthesis of indole-pyran hybrids **28**.

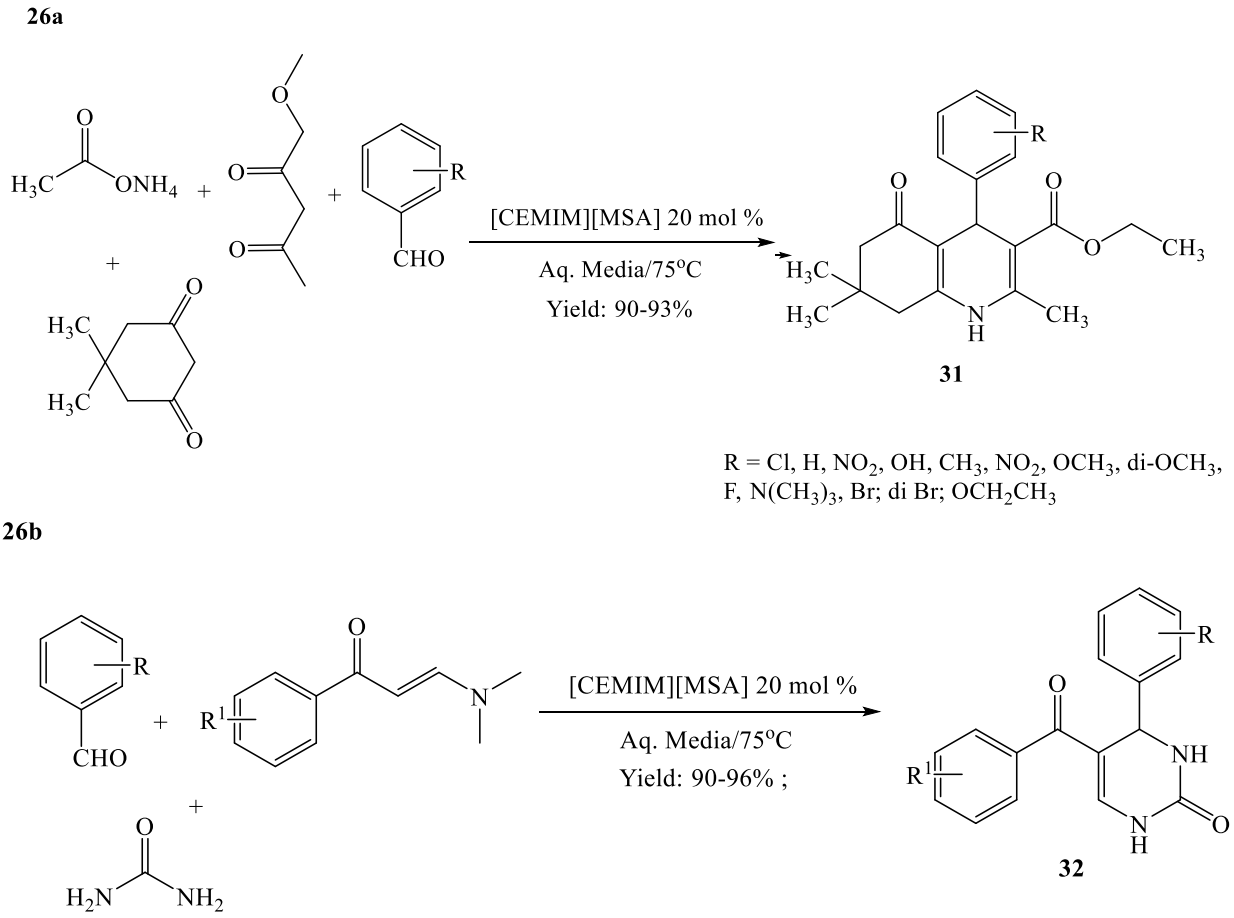
Kumar and co-workers described the regioselective formation of N-heterocyclic compounds **29** and **30** (Scheme 25) using CuO nanoparticles bounded with an ionic liquid, CuO[HN_{222}][Al_2Cl_7], as a recyclable nanocatalyst[35]. The synthesis is achieved through cross-coupling reactions between imidazole, adenine, benzimidazole, and aryl boronic acids, conducted in water without the need for bases or ligands. The study highlights the nanocatalyst's ability to deliver excellent yields (55–91%) within 3 hours, and its recyclability for up to five cycles with no reduction in activity. The catalytic system's efficiency arises from the ionic liquid's properties, which enhance surface area and catalytic activity. The protocol represents a greener alternative to traditional methods by avoiding harsh conditions and using eco-friendly solvents.



Scheme 25. Synthesis of N-heterocyclic compounds **29** and **30**.

Synthesis of polyhydroquinolines (Scheme 26a) and 6-unsubstituted dihydropyrimidinones (Scheme 26b) in the presence of ionic liquid, [CEMIM][MSA], catalyst was reported by Patil *et al*[36]. The [CEMIM][MSA]

ionic liquid was synthesized from economical raw materials under mild conditions and demonstrated excellent catalytic performance in aqueous media, enabling high yields of the target compounds without the need for purification. This method eliminates toxic organic solvents and minimizes waste. The synthesis was achieved through a multicomponent reaction, with the conditions optimized for maximum yield and efficiency. The study emphasizes the importance of using renewable materials and benign solvents in organic synthesis, contributing to the growing field of green chemistry.

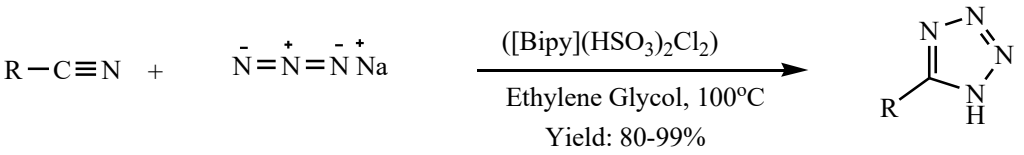


Scheme 26. Synthesis of polyhydroquinolines **31** and dihydropyrimidinones **32**.

32	R	R^1	32	R	R^1
a	4-Cl	H	**h**	3-CF_3	H
b	4-H	H	**i**	3-Cl	4-CH_3
c	4-OCH_3	H	**j**	3-F	4-CH_3
d	3-Cl	H	**k**	4-F	4-CH_3
e	3-F	H	**l**	3,4-CH_3	4-CH_3
f	4-F	H	**m**	3-CF_3	4-CH_3
g	3,4-CH_3	H	**n**	4-NO_2	4-NO_2

Aali and co-workers described the synthesis of tetrazoles **33** (Scheme 27) in the presence of IL, 1-disulfo-[2,2-bipyridine]-1,1-diium chloride ([BiPy]$(HSO_3)_2Cl_2$) as a catalyst[37]. The catalyst facilitates reaction

between nitriles and sodium azide, yielding tetrazole derivatives. Ethylene glycol, a green solvent, promoting an eco-friendly process with moderate conditions and lesser reaction times. The method is advantageous due to the catalyst's reusability, low cost, and ease of preparation. Moreover, the reaction shows broad substrate compatibility, effectively producing high yields of tetrazoles from aryl, heteroaryl, and alkyl nitriles. This approach offers an environmentally friendly alternative to traditional synthetic methods, avoiding toxic reagents and high temperatures, making it a promising tool in green chemistry.

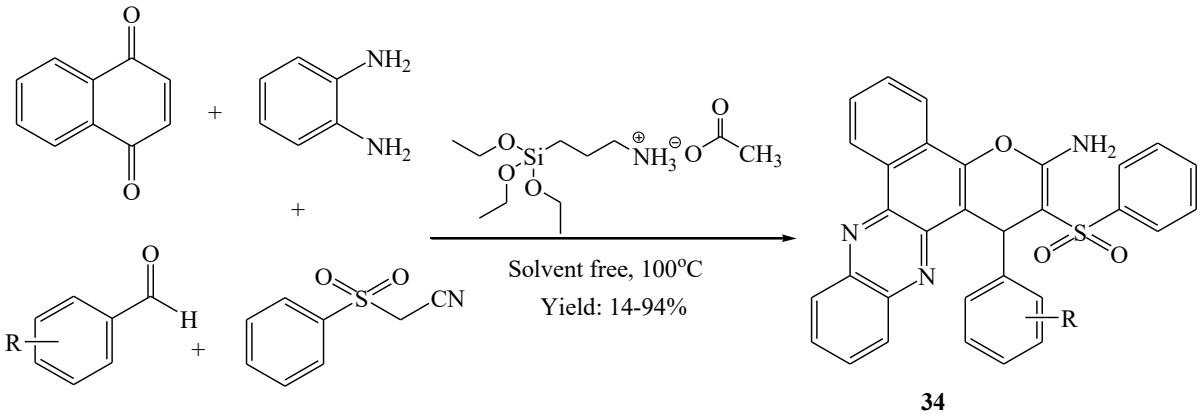


33

R = Ph; 4-CH_3Ph; 2-CH_3Ph; Butyl; propyl; thienyl; 4-ClPh; 2-NH_2Ph; 4-NH_2Ph; 2-NH_2-5-ClPh; 2-NH_2-5-NO_2Ph; 3,5-OMePh

Scheme 27. Synthesis of tetrazoles **33**.

A green and effective procedure was proposed by Shirzaei *et al.*[38] for synthesizing of 2-(phenylsulfonyl)-1*H*-benzo[a]pyrano[2,3-c]phenazin-3-amines **34** (Scheme 28). The synthesis was carried out through multicomponent reaction involving 2-hydroxynaphthalene-1,4-dione, aromatic aldehydes, o-phenylenediamine, and (phenylsulfonyl)acetonitrile. The process uses a new IL catalyst, $[(EtO)_3Si(CH_2)_3NH_3^+][CH_3COO^-]$. This ionic liquid offers advantages like high stability, reusability, and efficient catalytic activity, promoting a greener chemistry approach. Key aspects include simple reaction conditions, high yields, lesser reaction times, and environmentally friendly methods.



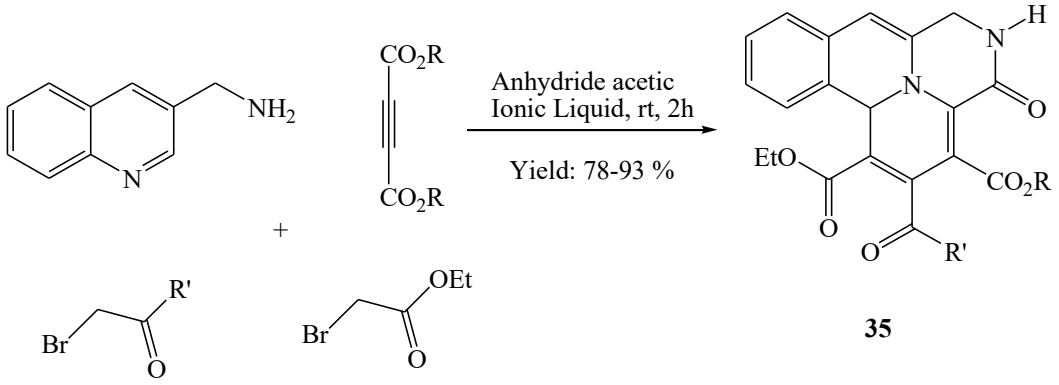
34

R = H; 2-NO_2; 3-NO_2; 2-Cl; 2,6-Cl; 4-Cl; 4-Br; 3-OH; 2,3-OCH_3; 3,4-OCH_3; 3,4,5-OCH_3

Scheme 28. Synthesis of 2-(phenylsulfonyl)-1*H*-benzo[a]pyrano[2,3-*c*]phenazin-3-amines **34**.

Sheikholeslami-Farahani *et al.* demonstrated the formation of pyrazinoquinazolines **35** (Scheme 29) using IL, specifically 1-octyl-3-methyl imidazolium bromide[39]. The reaction, conducted at room temperature, yielded high product efficiency. The synthesized compounds were evaluated for antioxidant activity, showing low DPPH radical scavenging but good ferric ion reducing power, particularly for one compound (**35b**). This

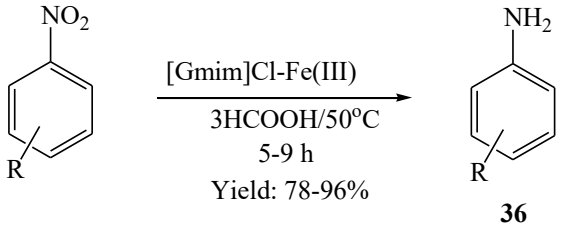
research highlights the advantages of ionic liquids, including high yield, easy product separation, and recyclability, making it an environmentally friendly method for synthesizing biologically active compounds.



R = Me, Et; R' = 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, COOEt

Scheme 29. Synthesis of pyrazinoquinazolines **35**.

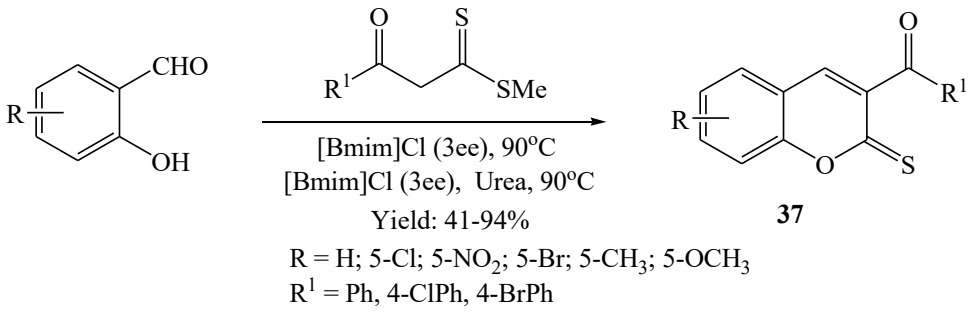
Deepa *et al.* presented a green and reusable iron-functionalized imidazolium-based, IL, catalyst for the reduction of nitroarenes to amines **36** (Scheme 30) using formic acid[40]. The process operates under mild conditions (50°C), offering high yields (up to 99%) and selectivity without the need for bases or external hydrogen sources. Iron is chosen for its abundance and eco-friendliness, making the catalyst both cost-effective and sustainable. The IL can be detached and recycled easily, making it suitable for industrial applications in producing amines used in drugs, agrochemicals, and dyes.



R = 2-Cl, 4-Cl, 3-Cl, 2-OH, 4-OH; 3-OH, 2-CO_2H, 4-CO_2H, 3-CO_2H, 2-CH_3, 4-CH_3, 3-CH_3; 2-OCH_3, 4-OCH_3, 3-OCH_3

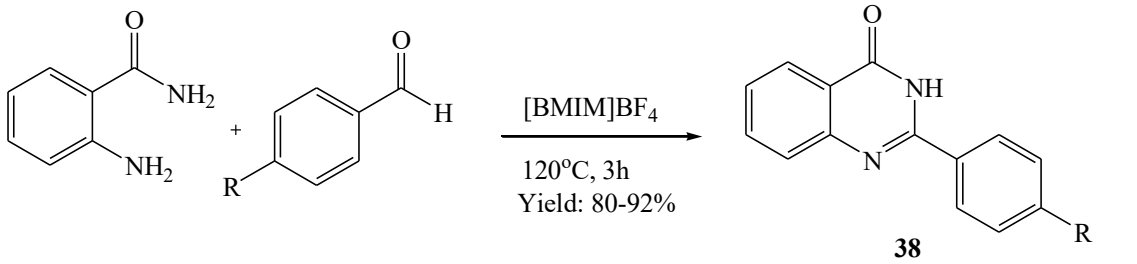
Scheme 30. Synthesis of amines **36**.

A catalyst-free method for synthesizing 2*H*-chromene-2-thiones **37** (Scheme 31) using salicylaldehydes and β-oxodithioesters in 1-butyl-3-methylimidazolium chloride ([Bmim]Cl) was reported by Sharma *et al.*[41]. By using 3 equivalents of [Bmim]Cl and a reaction temperature of 90°C, the authors achieved high yields (up to 94%) of the desired 2*H*-chromene-2-thiones. This process is efficient, environmentally friendly, and recyclable, making it a promising alternative for organic synthesis.



Scheme 31. Synthesis of 2*H*-chromene-2-thiones **37**.

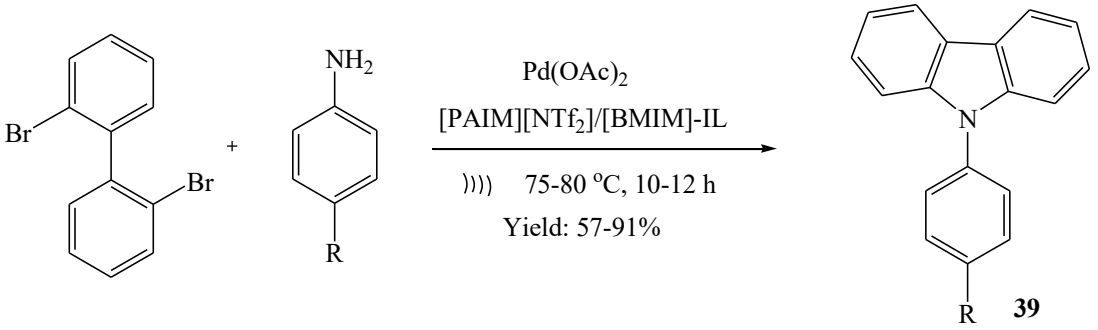
Ma *et al*[42] described the synthesis of quinazolin-4(3*H*)-ones **38** (Scheme 32) using an ionic liquid catalyst, 1-butyl-3-methylimida-zolium tetrafluoride ([Bmim]BF_4), which also served as the solvent. The reaction mixture of 2-aminobenzamides, aldehydes and [Bmim]BF_4 was heated at 120°C for 3 h under air conditions to obtain **38.** This protocol has the advantage of being solvent-free, resulting in a high product yield, with the catalyst remaining active and reusable for up to four cycles.



R = H, F, Cl, Br, CN, CF_3, Ph, CH_3, OCH_3

Scheme 32. Synthesis of quinazolin-4(3*H*)-ones **38**.

Synthesis of carbazoles **39** (Scheme 33) using an IL, [BMIM][BF_4], as a solvent and IL, [PAIM][NTf_2] as a promotor was described by Jamadar and co-workers.[43] To obtained the product **39**, a primary amine was reacted with 2,2'-dibromodiphenyl in presence of a $Pd(OAc)_2$ catalyst, [PAIM][NTf_2] as the ionic liquid (IL) promoter, and [BMIM][BF_4] as the IL solvent. The reaction was carried out under a nitrogen atmosphere at room temperature, with ultrasonication applied to the reaction mixture for 10-12 h at a temperature of 75-80 °C.



R= H, CH_3, OCH_3, Cl, NO_2

Scheme 33. Synthesis of carbazoles **39**.

2.3. Polyethylene glycols (PEGs)

PEG is a linear polymer produced by the polymerization of ethylene oxide. Lower molecular weight PEGs, for example PEG-200 and PEG-400 (with molecular weights of 200 and 400, respectively), are typically used as solvents because they remain liquid at room temperature[44-45]. In contrast, higher molecular weight PEGs, such as PEG-4000, are often utilized as supports in soluble polymer-supported chemistry[46-48], owing to their solid state at room temperature and a melting point of 61 °C.

PEG polymers dissolve readily in relatively polar solvents such as dimethylformamide, methanol, and water but remain insoluble in less polar solvents like diethyl ether and isopropanol. Due to their unique properties, PEGs have gained widespread use in organic synthesis. They are nonvolatile, recyclable, highly stable under both acidic and basic conditions, and capable of withstanding high temperatures. Additionally, they are readily available in large quantities at low cost.

PEGs are also notable for their ability to improve the solubility of hydrophobic drugs, thereby enhancing their bioavailability[49-50]. This versatility has made them an important tool in both chemical and pharmaceutical applications. However, despite their favourable physicochemical properties, PEGs have raised environmental concerns due to their limited biodegradability and recyclability, especially in the context of green chemistry and sustainable polymer design. Structurally, PEGs consist of repeating ethylene oxide units (–CH2–CH2–O–)n, with a chemically stable ether backbone that is resistant to microbial attack and hydrolysis. As a result, PEGs - particularly those with higher molecular weights - tend to be environmentally persistent and difficult to mineralize completely.

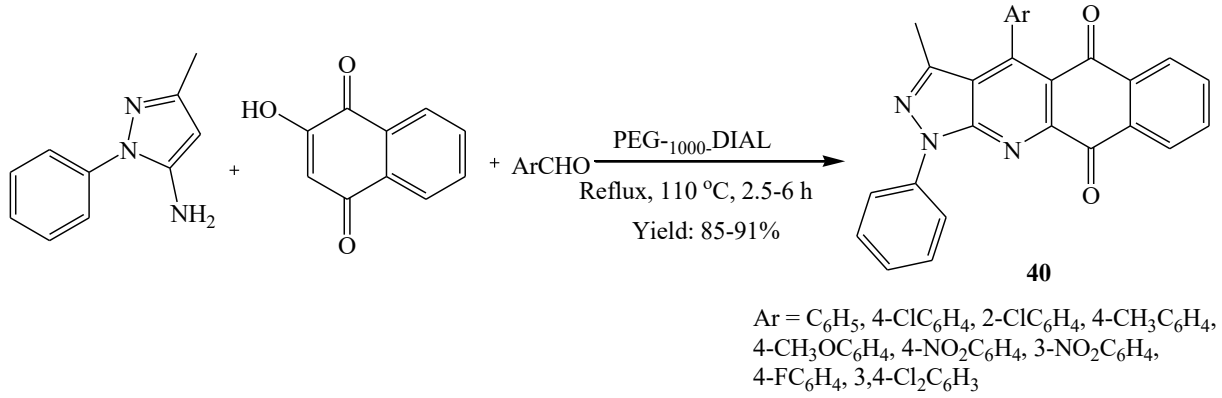
The biodegradability of PEGs largely depends on their molecular weight and environmental conditions.[51] PEGs with low molecular weights (typically below 1000 Da) can be partially degraded by certain microorganisms, such as Pseudomonas, Sphingomonads, and Mycobacterium species, primarily under aerobic conditions. Enzymes like alcohol dehydrogenases and peroxidases may facilitate the oxidation of terminal hydroxyl groups, initiating chain cleavage. However, complete mineralization into carbon dioxide and water is rare, and partial degradation often results in oligomers or intermediate compounds like aldehydes and peroxides, which may pose ecotoxicological risks.

On the recyclability front, PEGs pose a challenge due to their predominant use in liquid or solution-phase formulations,[42-54] which limits mechanical recycling. Chemical recycling methods have been investigated to recover monomeric ethylene glycol or lower oligomers via depolymerisation processes. These include catalytic cracking, oxidative cleavage, and hydrothermal treatment, although such approaches often require high energy input and stringent control to avoid the formation of harmful by-products. Thermal degradation of PEGs through pyrolysis yields volatile compounds like acetaldehyde and formaldehyde, but this approach is not widely implemented due to environmental and safety concerns. In response, recent research has focused on designing PEG derivatives with built-in cleavable linkages (e.g. esters, carbonates, peptides) that facilitate breakdown under physiological or environmental triggers, aligning with circular economy principles.

To address the limitations of PEGs, biodegradable alternatives and copolymers have been developed, such as PEG-polylactide (PEG-PLA), PEG-polycaprolactone (PEG-PCL), and PEG-carbonates, which combine PEG's solubility with the degradability of aliphatic polyesters or carbonates. These materials can undergo enzymatic or hydrolytic degradation more readily and are being explored for drug delivery, biomedical applications, and sustainable materials. Additionally, life cycle assessments (LCA) and environmental fate studies are increasingly being employed to evaluate the long-term impact of PEGs and their alternatives. In conclusion, while PEGs are not readily biodegradable or recyclable in their native form, advancements in polymer chemistry, enzymatic degradation strategies, and design for end-of-life degradation are paving the

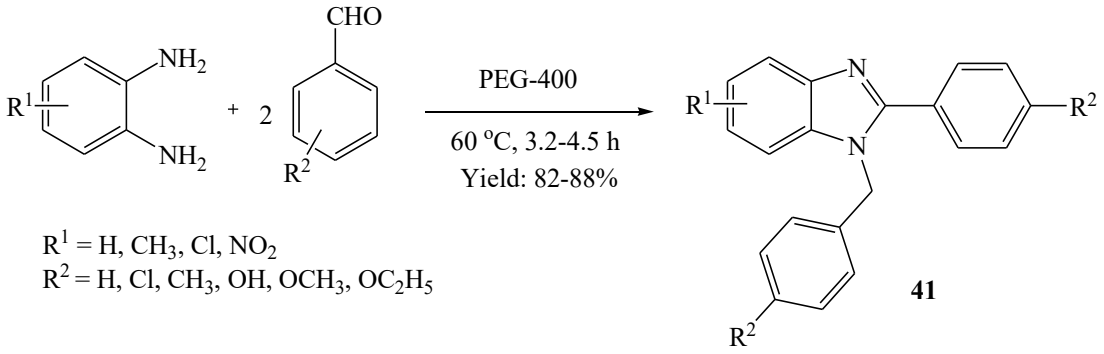
way toward more sustainable use and disposal of PEG-based systems in both industrial and biomedical sectors.

Ren et al.[55] described the synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[h]pyrazolo[3,4-b]quinoline-5,10-diones **40** (Scheme 34) through a single-step reaction involving aromatic aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, and 2-hydroxynaphthalene-1,4-dione. The reaction was catalyzed by a PEG1000-based dicationic acidic ionic liquid (PEG1000-DAIL) by refluxing the reaction mixture in toluene for 2.5 to 6 h at 110 °C. This protocol has numerous advantages, including high yields, easy workup, and the ability to recover and reuse the catalyst.



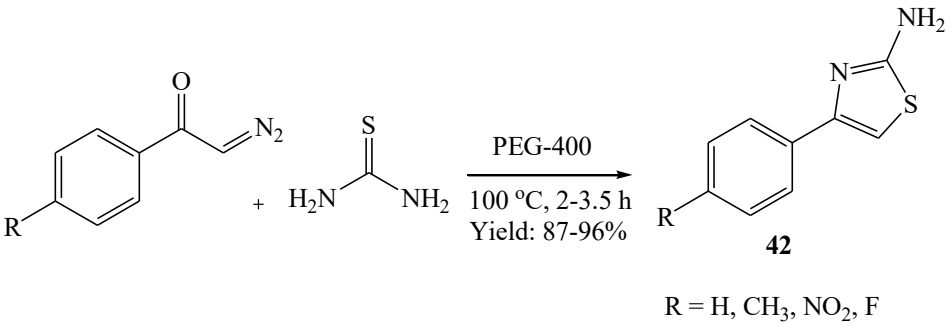
Scheme 34. Synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[h]pyrazolo[3,4-b]quinoline-5,10-diones **40.**

Mekala *et al* described the synthesis of benzimidazoles **41** (Scheme 35) *via* the reaction of o-phenylenediamine and aldehydes in PEG-400 as a solvent at 60 °C.[56] This protocol has the advantage of less expensive, operational simplicity and high yields.



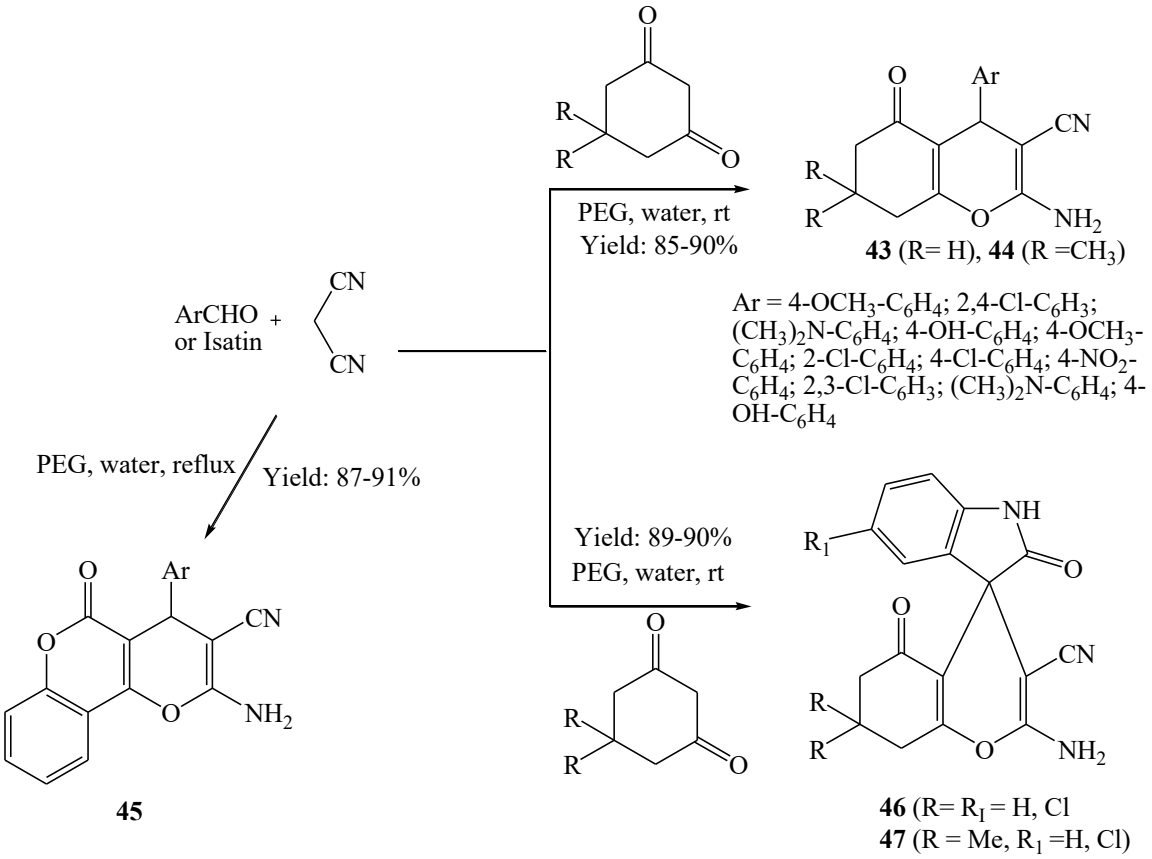
Scheme 35. Synthesis of benzimidazoles **41**.

Babu *et al*[57] have reported the preparation of 2-aminothiazoles **42** (Scheme 36) *via* reaction of α-diazoketones and thiourea in PEG-400 solvent system by heating the mixture at 100 °C for 2 to 3.5 h. This method is straightforward, rapid, and efficiently produces product in high yields.



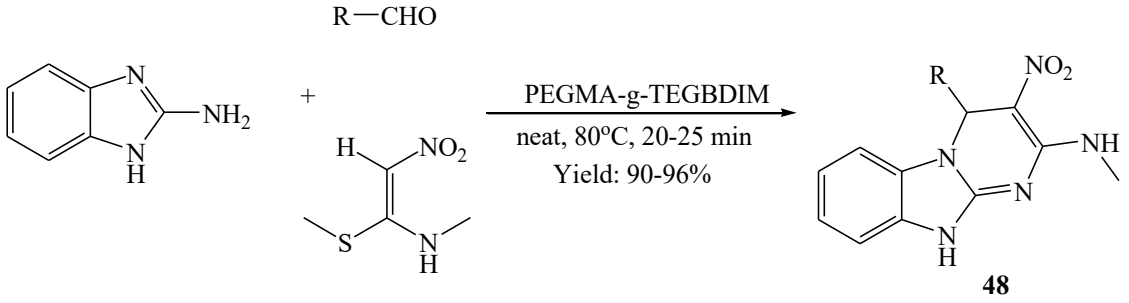
Scheme 36. Synthesis of 2-aminothiazoles **42**.

A research by Survase and co-workers described the multicomponent synthesis of 4*H*-pyran derivatives, including 4-phenyl-4*H*-pyrans **43-44**, spirochromenes **45**, and dihydropyrano[3,2-c]chromines **46-47**, (Scheme 37) using PEG-600 in aqueous medium[58]. The reaction involves the condensation of aromatic aldehydes, malononitrile, and cyclic 1,3-dione or 4-hydroxycoumarin, proceeding under mild conditions. The process yields high product efficiency with ease of product isolation, all while adhering to green chemistry principles. PEG-water as a solvent facilitates the recyclability of the medium, reduces waste, and eliminates the need for toxic organic solvents or catalysts. Overall, this efficient and environmentally sustainable approach offers a cleaner reaction profile for synthesizing medicinally significant 4*H*-pyran derivatives.



Scheme 37. Synthesis of 4*H*-pyran derivatives **43-47**.

Reddy *et al* described the formation of aryl-benzo[4,5]imidazo[1,2-*a*]pyrimidine amines **48** (Scheme 38)[59] under solvent-free conditions. This method aligns with green chemistry principles, providing high yields, reusability, and minimal environmental impact. The catalyst remained effective even after seven reaction cycles, making it a cost-efficient and environmentally-friendly option for organic synthesis, particularly in pharmaceutical applications.

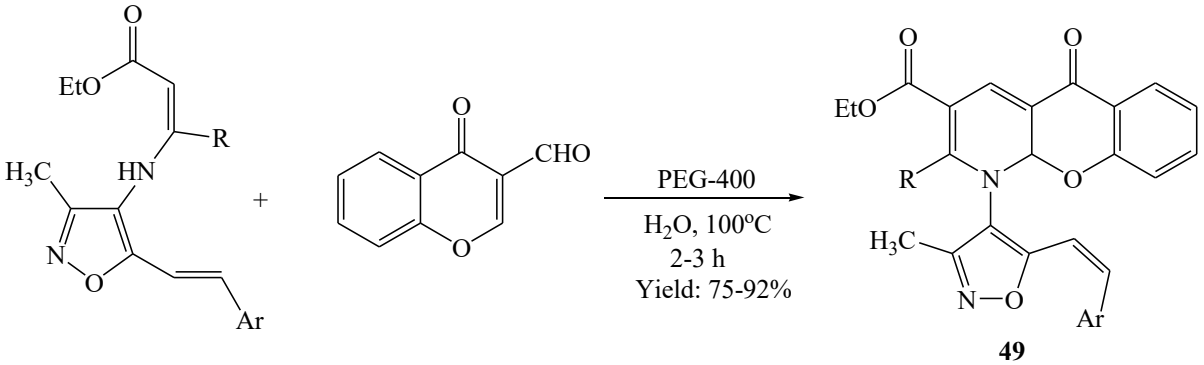


48

R = 4-BrPh; 3-BrPh; 2-MePh; 4-ClPh; 3-ClPh; 2-OHPh; 4-FPh, 3-FPh; 2-OMePh; 4-MePh; 3-MePh; pyridine; 4-OEtPh; 2-BrPh; Thiophene; 4-OHPh; 2-ClPh; 4-NO_2Ph; 2-F; 5-BrPh

Scheme 38. Synthesis of aryl-benzo[4,5]imidazo[1,2-*a*]pyrimidine amines **48**.

Ponduri *et al* reported the formation of isoxazole-substituted chromeno[2,3-*b*]pyridines **49** (Scheme 39). The reaction involves isoxazolyl enamino esters and 3-formylchromones in aqueous medium and PEG-400, environment-friendly solvents and promoters[60]. The study explores various catalysts, solvents, and conditions, concluding that the optimal reaction occurs in a PEG-400 and water mixture (1:9 ratio) at 100°C, yielding up to 88% of the target compounds. The study highlights the process's simplicity, high yields, and its contribution to green chemistry by eliminating toxic metals and reducing waste, while also proposing a plausible reaction mechanism involving cyclization and intermediate formation.

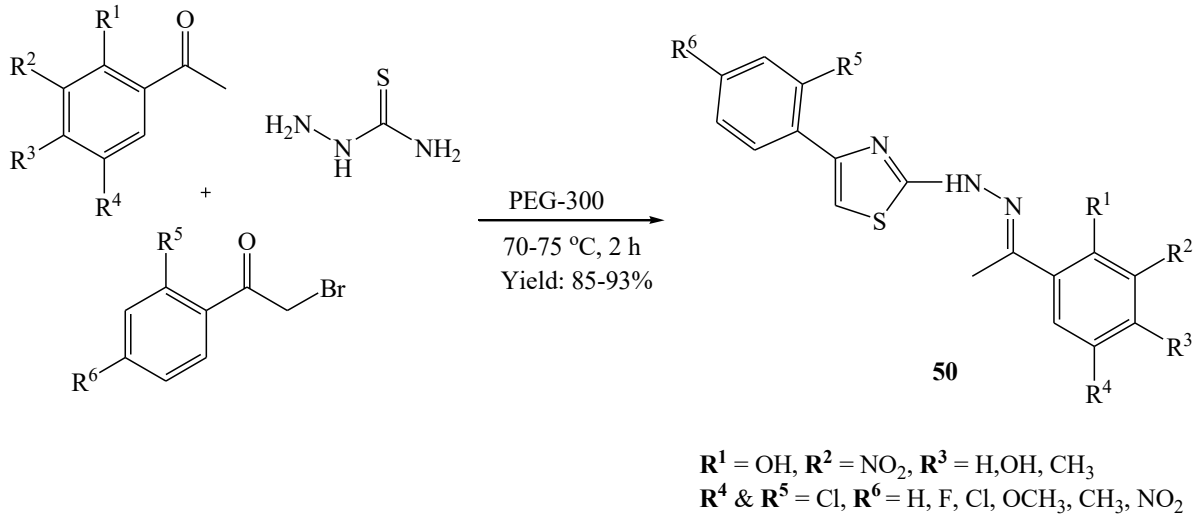


49

Scheme 39. Synthesis of isoxazole-substituted chromeno[2,3-*b*]pyridines **49**.

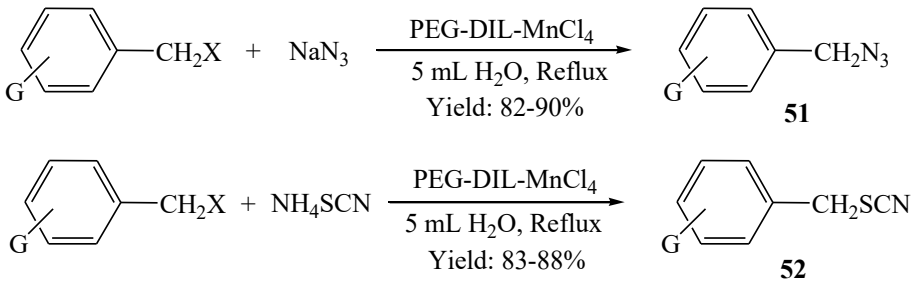
49	Ar	R	49	Ar	R
a	C_6H_5	CH_3	J	4-$N(CH_3)_2C_6H_4$	CH_3
b	4-ClC_6H_4	CH_3	K	4-ClC_6H_4	C_6H_5
c	2-ClC_6H_4	CH_3	L	2-ClC_6H_4	4-ClC_6H_4
d	4-BrC_6H_4	CH_3	M	2,4-$Cl_2C_6H_4$	4-$CH_3C_6H_4$
e	2-BrC_6H_4	CH_3	N	2-$OCH_3C_6H_3$	4-BrC_6H_4
f	4-FC_6H_4	CH_3	O	2-$CH_3C_6H_4$	4-$CH_3C_6H_4$
g	4-$NO_2C_6H_4$	CH_3	P	2-Furyl	CH_3
h	4-$CH_3C_6H_4$	CH_3	Q	2-Thienyl	CH_3
i	4-$OCH_3C_6H_4$	CH_3	R	3-Pyridyl	CH_3

Raut and Bhosale[61] reported the production of 2-(2-hydrazinyl)thiazoles **50** (Scheme 40) by heating a reaction mixture of acetophenones and thiosemicarbazide in PEG-300 with 2-3 drops of acetic acid at 70-75 °C for 60-90 min. Subsequently, α-bromoketones were added gradually over 5-10 minutes, and the mixture was further heated for an additional 15 minutes.

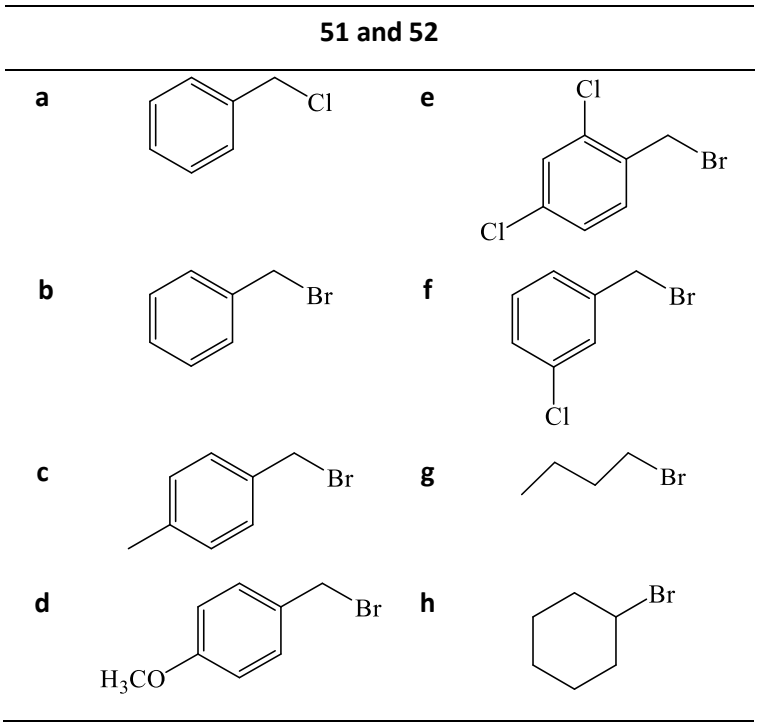


Scheme 40. Synthesis of 2-(2-hydrazinyl)thiazoles **50**.

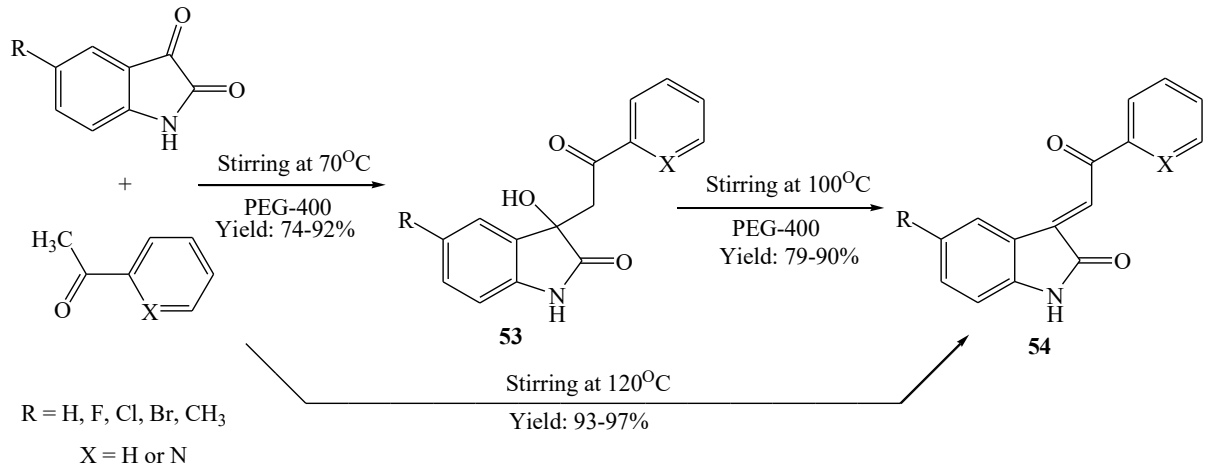
A research by Goodajdar *et al*. introduces a novel phase transfer catalyst (PTC), PEG-DIL-based $MnCl_4^{2-}$, synthesized from poly(ethylene glycol) dichloride, methylimidazole, and $MnCl_2$.[62] It effectively catalyzed nucleophilic substitution reactions of benzyl halides in water, producing benzyl azides **51** and thiocyanates **52** (Scheme 41) with high yields. Its dicationic nature facilitates ion transfer, while the Mn^{2+} center accelerates the reaction. This method is environmentally friendly, using water as a solvent, and the catalyst is thermally stable and reusable.



Scheme 41. Synthesis of benzyl azides **51** and thiocyanates **52**.



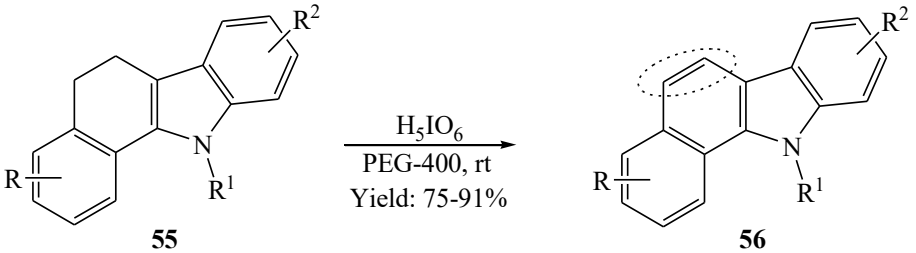
Gupta *et al* described an eco-friendly method for synthesis of chalcones **54** as well as 3-hydroxy precursors **53** (Scheme 42) using PEG-400 as a green solvent and phase-transfer catalyst[63]. The one-pot process, which avoids harmful solvents and catalysts, efficiently produces 3-hydroxy-2-oxindoles and their chalcones with excellent yields and reduced reaction times. PEG 400 is recyclable, non-toxic, and improves the reaction's sustainability. This method is an environmentally superior alternative to conventional synthesis, offering broad applicability for creating bioactive compounds.



Scheme 42. Synthesis of chalcones **54**

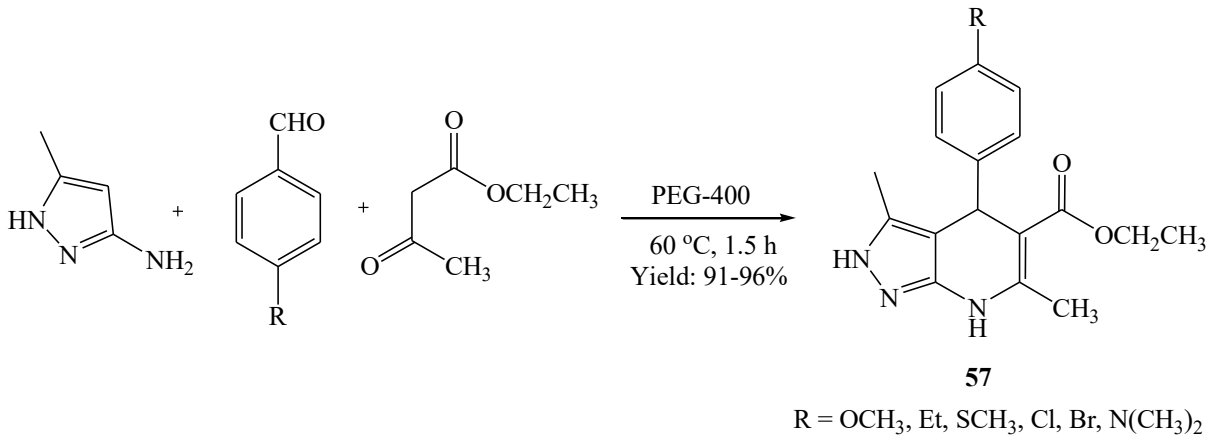
53 and **54**	**X**	**Ar**	**53** and **54**	**X**	**Ar**
a	H	Phenyl	**f**	H	2-Pyridyl
b	F	Phenyl	**g**	F	2-Pyridyl
c	Cl	Phenyl	**h**	Cl	2-Pyridyl
d	Br	Phenyl	**i**	Br	2-Pyridyl
e	CH_3	Phenyl	**j**	CH_3	2-Pyridyl

Ghom and co-workers reported a green method for the regioselective iodination of dihydrobenzo[*a*]carbazoles to yield iodo-products **56** (Scheme 43) using periodic acid in PEG-400[64]. This method replaces conventional processes, offering a mild reaction condition with high regioselectivity, excellent yields, and reusable PEG-400 solvent, enhancing the process's eco-friendliness. The study investigates the role of oxidizing agents and optimizes reaction conditions to achieve high yields of iodinated products. The process shows tolerance to various functional groups and is scalable with solvent reusability up to five times.



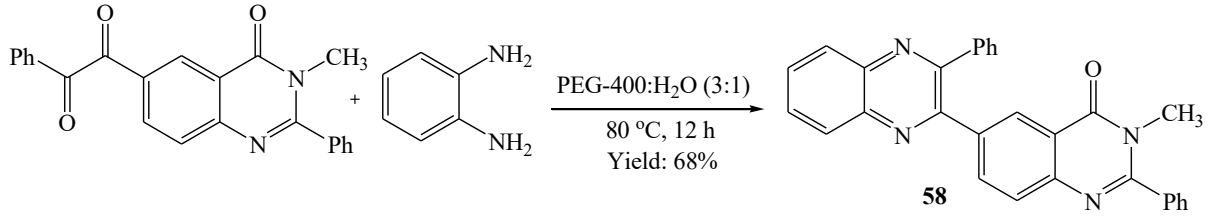
Scheme 43. Synthesis of iodo-dihydrobenzo[*a*]carbazoles **56.**

Kerru and co-workers[65] described the formation of 3,6-dimethyl-4,7-dihydro-2*H*-pyrazolo[3,4-b]pyridines-5-carboxylate **57** (Scheme 44) through a multicomponent reaction of 1*H*-pyrazol-3-amino-5-methyl, substituted aromatic aldehydes, and ethyl acetoacetate in PEG-400 as a solvent at 60 °C. This method has the advantages of a simple procedure, the use of non-hazardous solvents, and high yields of products.



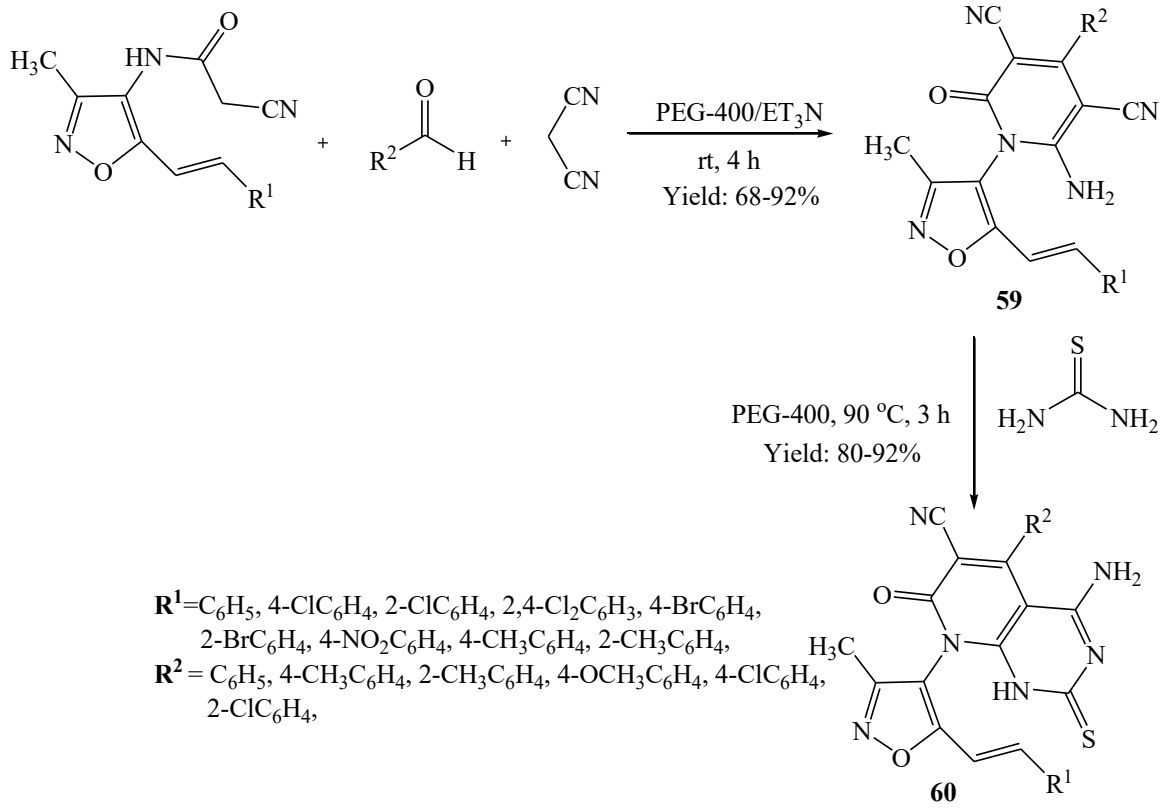
Scheme 44. Synthesis of 3,6-dimethyl-4,7-dihydro-2*H*-pyrazolo[3,4-b]pyridines-5-carboxylate **57**.

Pagilla and co-workers[66] reported the synthesis of 3-methyl-2-phenyl-6-(3-phenylquinoxalin-2-yl)quinazolin-4(3*H*)-one **58** (Scheme 45) by reacting 1-(3-methyl-4-oxo-2-phenyl-3,4-dihydroquinazolin-6-yl)-2-phenylethane-1,2-dione with benzene-1,2-diamine. The reaction was carried out in a 3:1 volume ratio of PEG-400 and water at 80°C for 12 h under stirring.



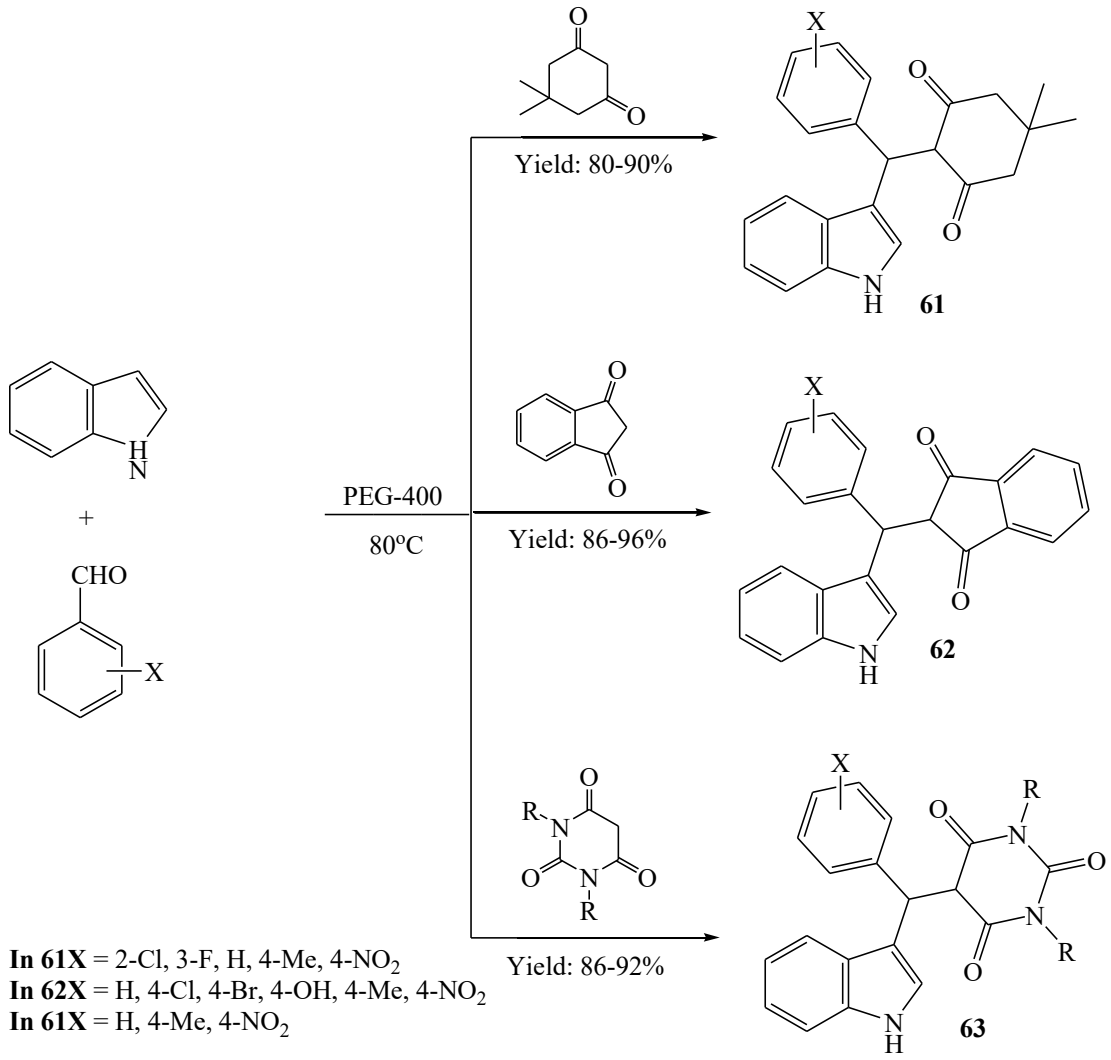
Scheme 45. Synthesis of 3-methyl-2-phenyl-6-(3-phenylquinoxalin-2-yl)quinazolin-4(3*H*)-one **58**.

Dasari *et al* have reported the formation of new isoxazolyl pyrido[2,3-d]pyrimidine **60** (Scheme 46) in polyethylene glycol-400[67]. The reaction of isoxazolyl cyanoacetamide synthon with aromatic aldehydes and malononitrile was conducted at room temperature using triethylamine (Et_3N). This process yielded the corresponding (E)-6-amino-1-(3-methyl-5-styrylisoxazol-4-yl)-2-oxo-4-phenyl-1,2-dihydro-pyridine-3,5dicarbonitrile **59** in the presence polyethylene glycol-400 (PEG-400). Furthermore, reaction of **59** with thiourea at 90°C in the presence of polyethylene glycol-400 (PEG-400) resulted in the formation of isoxazolyl pyrido[2,3-d]pyrimidines **60**. The protocol has operational simplicity, catalyst-free, environmentally safe, has a wide substrate scope, yields good results, and allows for the recovery and reuse of polyethylene glycol-400. Most importantly, it is environmentally friendly.



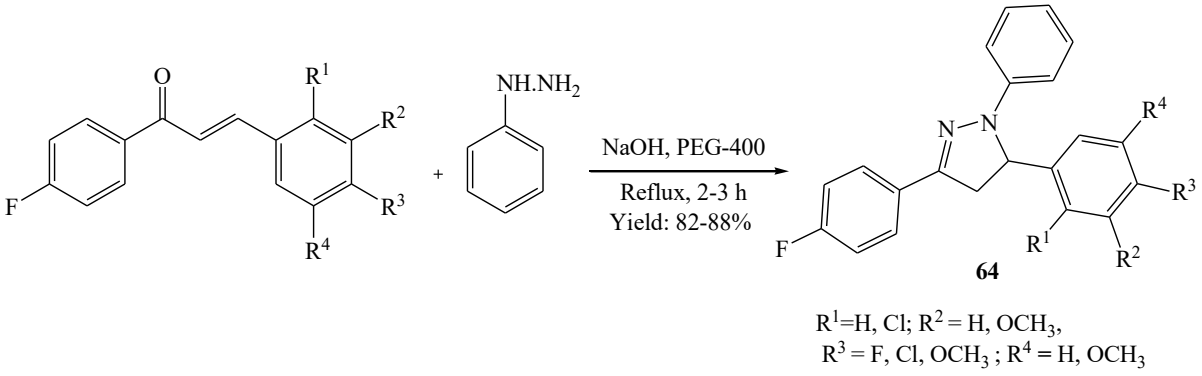
Scheme 46. Synthesis of isoxazolyl pyrido[2,3-*d*]pyrimidine **60**.

Synthesis of 3-substituted indoles **61-63** (Scheme 47) through a single-step, three-component condensation of indole, aromatic aldehydes, and CH-activated acids in the presence of PEG-400 was reported by Kardooni *et al*.[68] The reaction yields 3-substituted indoles with high selectivity, avoiding unwanted homodimer products such as bisindoles. The protocol achieves excellent yields at 80 °C, and PEG-400's unique ability to form hydrogen bonds with reactants facilitates efficient product formation. This environmentally friendly approach circumvents costly or poisonous catalysts and volatile organic solvents, offering a nontoxic and more ecological method for formation of bioactive indole derivatives.



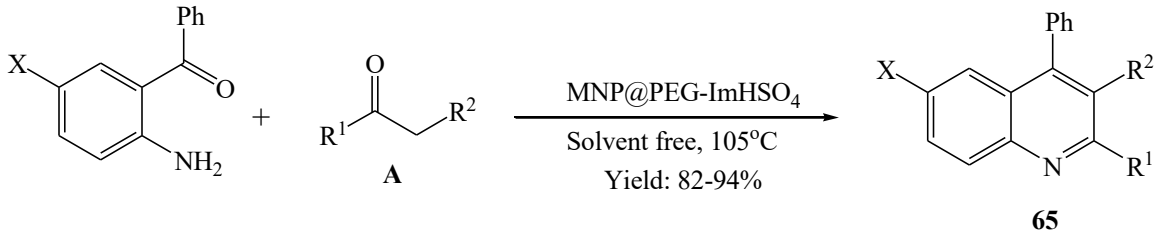
Scheme 47. Synthesis of 3-substituted indoles **61-63**.

Synthesis of pyrazoles **64** (Scheme 48) *via* the reaction of chalcones and phenylhydrazine in refluxing PEG-400 using 10% NaOH was described by Pathade and co-workers[69]. Environmental sustainability, affordability, high efficiency, and reusability are the key features of this PEG-400 method.

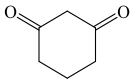
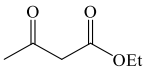
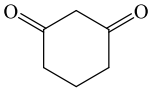
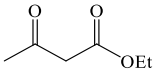
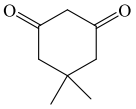
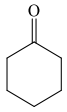
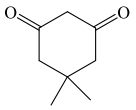
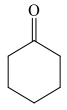
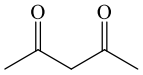
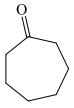
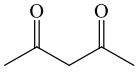
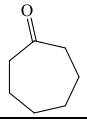


Scheme 48. Synthesis of pyrazoles **64**.

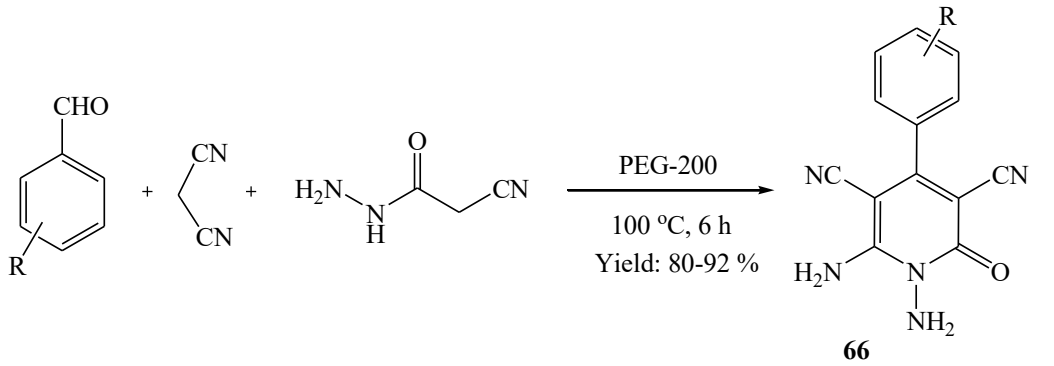
Fallah-Mehrjardi *et al*. prepared an ionic liquid (MNP@PEG-ImHSO$_4$) supported on magnetic nanoparticles for the synthesis of quinolones **65** (Scheme 49).[70] The catalyst was used for the condensation of 2-aminoaryl ketones and α-methylene ketones under solvent-free conditions. It demonstrated high yields, convenient magnetic separation, and excellent reusability over five cycles with no significant loss in activity. The process is green, avoiding hazardous solvents and reagents, making it a sustainable method for quinoline synthesis.



Scheme 49. Synthesis of quinolones **65**.

65	X	A	65	X	A
a	H		g	H	
b	Cl		h	Cl	
c	H		i	H	
d	Cl		j	Cl	
e	H		k	H	
f	Cl		l	Cl	

Das *et al.*[71] have successfully developed a method for synthesizing 1,6-diamino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **66** (Scheme 50). This method involves the reaction of various aldehydes, malononitrile, and cyanoacetohydrazide in PEG-200 solvent at 100°C for 6 h. Notably, this protocol makes use of biodegradable, non-toxic and recyclable PEG-200 as a catalyst and solvent, offering both environmental and practical advantages.

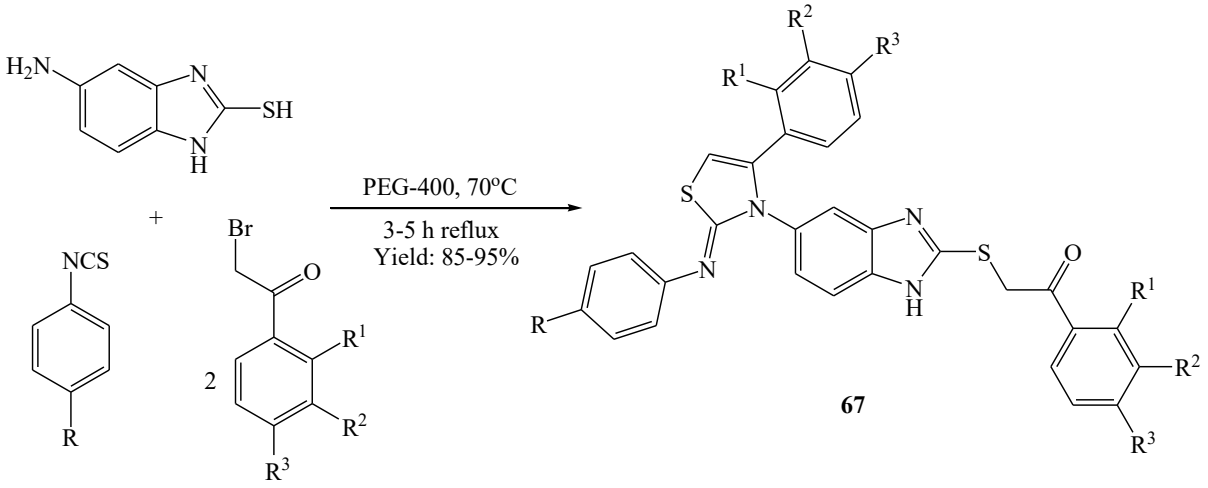


66

R = H, 4-F, 2-NO_2, 4-NO_2, 4-Br, 3-NO_2

Scheme 50. Synthesis of 1,6-diamino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **66**.

Chedupaka *et al* reported the formation of benzimidazole-based thiazoles **67** (Scheme 51) through a novel multicomponent reaction between 5-amino-2-mercaptobenzimidazole, substituted phenacyl bromides and phenyl isothiocyanates[72]. The reaction employs polyethylene glycol (PEG-400) as a green solvent, enabling a faster reaction with no by-product formation. The study also investigates the α-amylase inhibition activity of these compounds, with compounds **67d**, **67c**, **67h**, **67j**, and **67b** showing significant inhibitory effects, suggesting potential for antidiabetic activity. Molecular docking studies supported these findings, revealing strong binding interactions between the synthesized compounds and human pancreatic α-amylase, particularly compounds 4d and 4c, which displayed stable binding patterns. The work also includes structure-activity relationship (SAR) studies, indicating that halogen-substituted derivatives exhibited enhanced inhibitory activity.



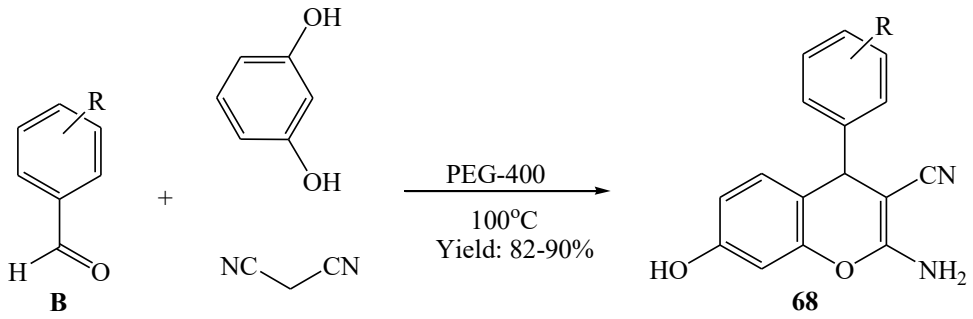
67

R = H, F; R^1 = H, F; R^2 = H, Cl; R^3 = H, F, Cl, Br, CH_3, NO_2, OMe, Ph

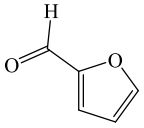
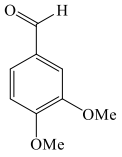
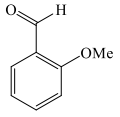
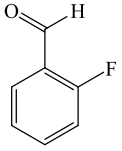
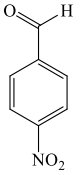
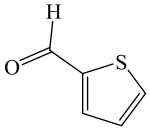
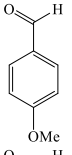
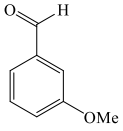
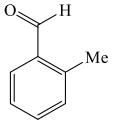
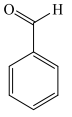
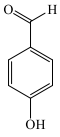
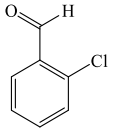
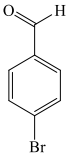
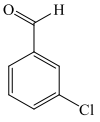
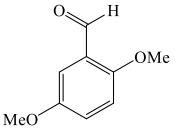
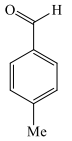
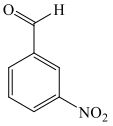
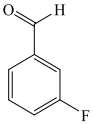
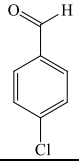
Scheme 51. Synthesis of benzimidazole-based thiazoles **67**.

Mohamadpour *et al*. reported the formation of 2-amino-4*H*-chromenes **68** (Scheme 52) *via* a Knoevenagel-Michael cyclocondensation reaction. This process utilizes aldehydes, malononitrile, and resorcinol in polyethylene glycol (PEG-400) which serves as both a solvent and catalyst[73]. The process offers

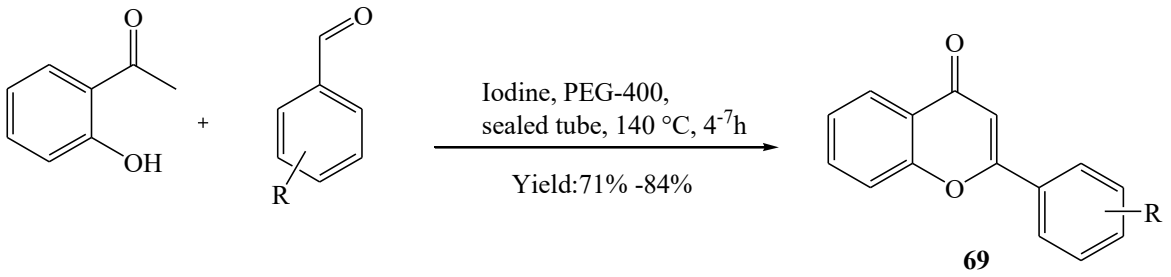
several green chemistry advantages, including easy workup without the need for toxic solvents or chromatographic separation, and the use of eco-friendly reagents. PEG-400 proved highly reusable, maintaining catalytic activity for at least four runs with minimal loss of efficiency. The study highlights PEG-400's as an environmentally friendly alternate to traditional solvents in synthetic chemistry.



Scheme 52. Synthesis of 2-amino-4*H*-chromenes **68**.

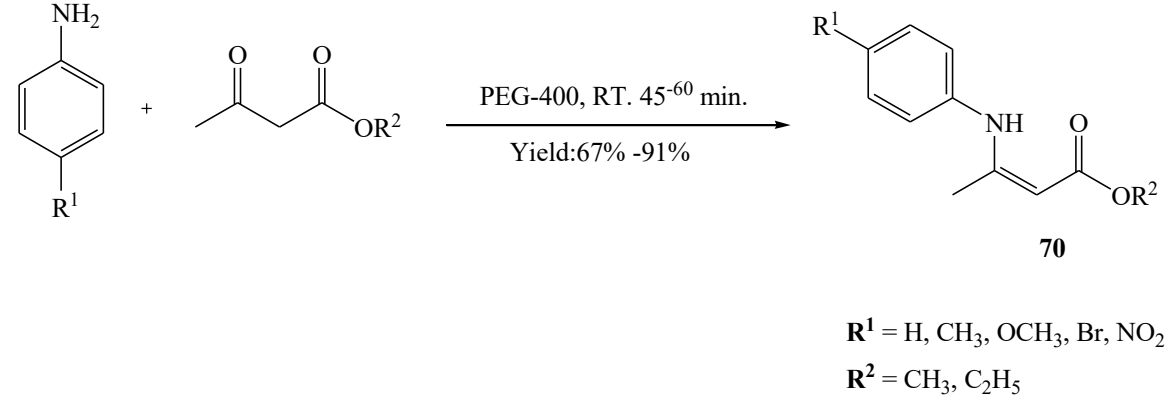
68	B	68	B	68	B
a		H		N	
B		I		O	
C		J		P	
D		K		Q	
E		L		r	
F		M		s	
G					

Kumar *et al*[74] have reported the synthesis of Flavones **69** *via* the reaction of 2-hydroxyacetophenone with benzaldehydes in the presence of Iodine as a catalyst and PEG-400 as a solvent by heating the reaction mixture at 140 °C for 4 to 7h (Scheme 53). This method has the advantages of being metal-free, single-step, Broad substrate scope with high yields as compared to Traditional synthetic methods, which often require toxic metal catalysts or harsh conditions.



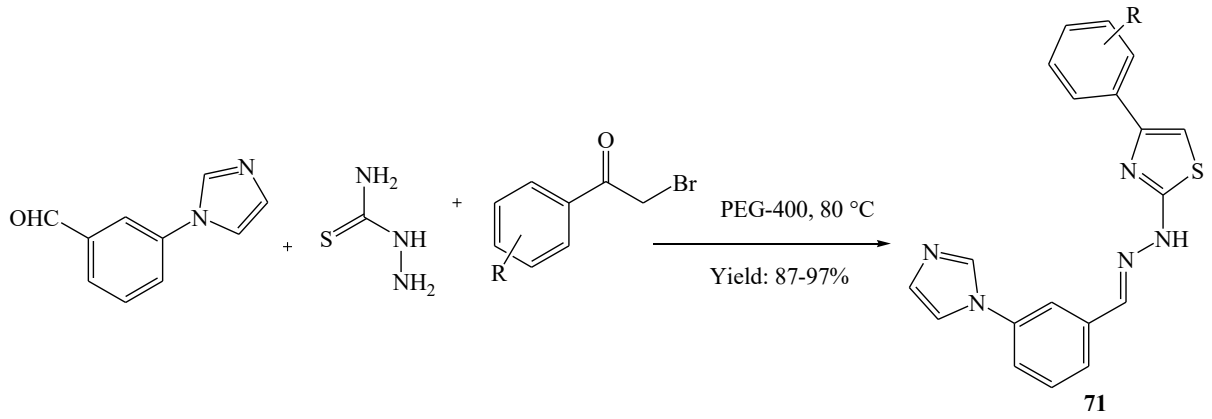
Scheme 53. Synthesis of flavones **69**.

Mukhedkar *et al* have reported the synthesis of β-enaminoesters **70** *by* grinding the reaction mixture of β-ketoesters and amines (Scheme 54) at room temperature for 45-60 min.[75] in the presence of PEG-400, which acts as both a catalyst and a solvent. This method has the advantages of Short reaction times, moderate to high yields (67 to 91%), recyclable solvent (PEG-400 reused up to five times with minimal loss in activity), simple work-up, and mild conditions.



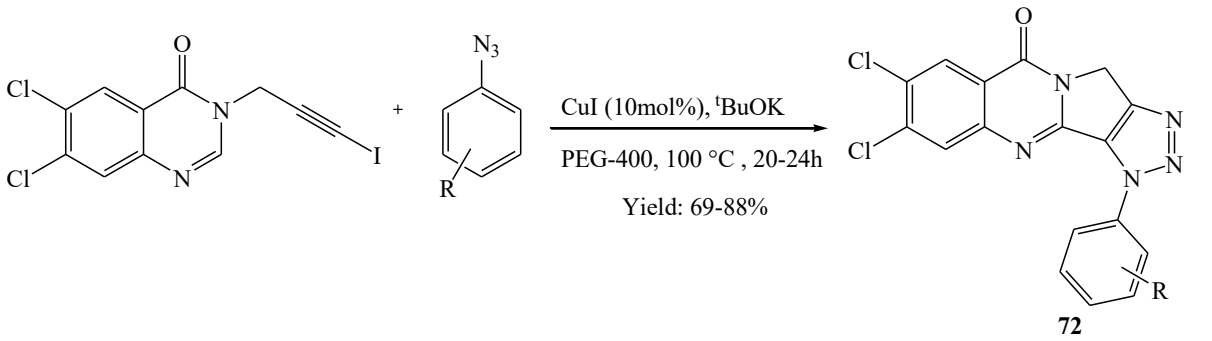
Scheme 54. Synthesis of β-enaminoesters **70**.

Single step synthesis of 2-(2-(3-(1*H*-imidazol-1-yl)benzylidene)Hydrazineyl)-4-(substitutedphenyl) thiazoles by stirring the reaction mixture of 3-(1*H*-imidazol-1-yl)benzaldehyde, thiosemicarbazide, and phenacyl bromides in PEG-400 (Scheme 55), at 80 °C for 12h has been reported by Vaidya *et* al.[76] The process offers several green chemistry advantages, including mild conditions without metal catalysts or additives and a high yield of products (87-97%). PEG-400 proved highly reusable, maintaining catalytic activity for at least five times with minimal loss of efficiency.



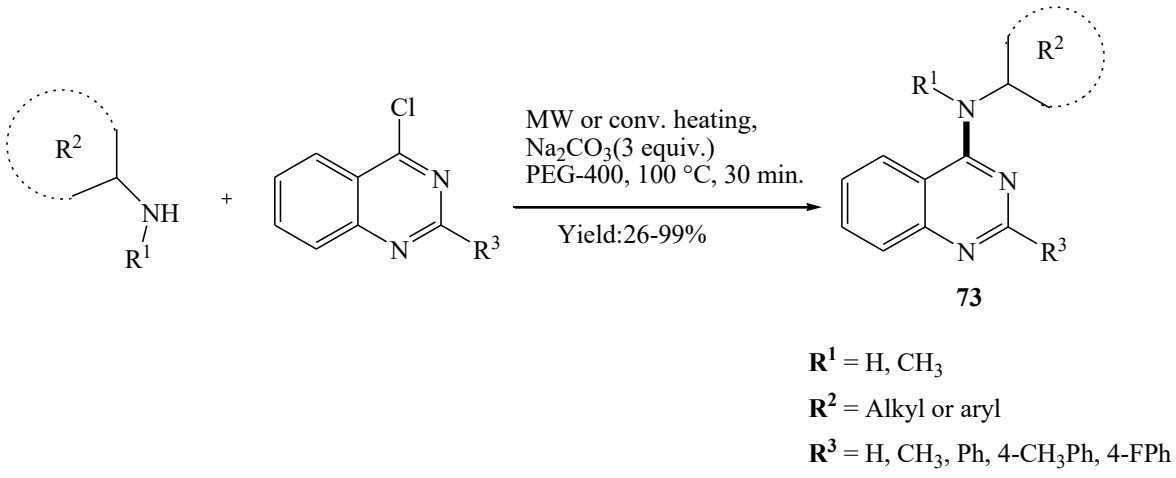
Scheme 55. Synthesis 2-(2-(3-(1*H*-imidazol-1-yl)benzylidene)hydrazineyl)-4-(substitutedphenyl)thiazoles **71**.

The synthesis of fused [1,2,3]triazolo [4',5':3,4]pyrrolo[2,1-*b*]quinazolinones **72** (Scheme 56) has been reported by Udayasree *et al*[77]. This was achieved through a [3+2] cycloaddition reaction of 6,7-dichloro-3-(3-iodoprop-2-yn-1-yl)quinazolin-4(3*H*)-one with aryl azides, catalysed by copper iodide (CuI) in the presence of potassium tert-butoxide (tBuOK) as a base by agitated the reaction mixture in a PEG-400 medium at 100 °C for 20 to 24 h.



Scheme 56. Synthesis of fused [1,2,3]triazolo [4',5':3,4]pyrrolo[2,1-*b*]quinazolinones **72**.

Synthesis of 4-aminoquinazolines **73** *via* the reaction of amines and quinolones by heating the reaction mixture at 100 °C under microwave irradiation(MW) or by conventional heating for 30 min. using PEG-400 as a green solvent (Scheme 57) in the presence of potassium carbonate as a base has been reported by de Paula Bueno *et* al.[78] This method has the advantages of being environmentally friendly (avoids toxic solvents), operationally simple and scalable, tolerates various functional groups on both aryl and alkyl halides, and provides moderate to excellent yields. This approach also facilitated the synthesis of Verubulin, a promising cancer treatment and a novel drug analogue, emphasizing its potential for sustainable drug discovery.



Scheme 57. Synthesis of 4-aminoquinazolines **73**.

2.4. Biocatalysis

Enzymes are non-toxic catalysts that operate with high selectivity at moderate reaction conditions, reducing energy consumption. They are increasingly being used in biotransformation for the preparation of chiral building blocks due to their high selectivity and potential to reduce the use of metals and organic solvents. This makes them advantageous for green synthesis and beneficial in chemical and pharmaceutical industries, as well as in medicine for analytical and diagnostic purposes.

Biological approaches offer numerous advantages, including: elimination of harmful chemicals and pollutants; cost-effectiveness and affordability; high biocompatibility and environmental safety; production of pure compounds with high yields and no by-products; diverse precursors sourced from natural organisms.[79-80] These attributes make biological protocols a perfect match for the principles of green chemistry.[81] For instance, islatravir, an HIV inhibitor, was entirely synthesized through biocatalysis.[82] Biocatalytic cells, abundant in natural enzymes, act as powerful agents for various biotransformations, applicable to both natural and synthetic targets.[83-84]

Several classes of enzymes are commonly employed in biocatalysis. Lipases are among the most widely used, catalyzing esterification, transesterification, and hydrolysis reactions in both aqueous and organic media.[85-86] They are particularly notable for their stability in non-aqueous solvents and have been applied in biodiesel production and the synthesis of optically active esters. Oxidoreductases, including alcohol dehydrogenases and monooxygenases, catalyze oxidation-reduction reactions and are important in producing chiral alcohols and epoxides.[87-88] Hydrolases (e.g., proteases, esterases), lyases, transferases, and isomerases are also utilized across various biotransformations.

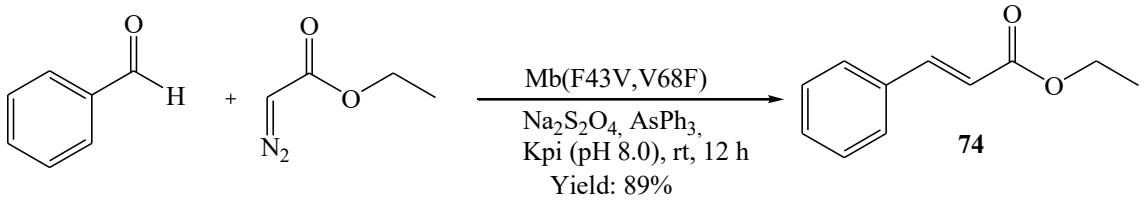
Despite these advantages, several challenges hinder the broader industrial adoption of biocatalysis. One of the primary concerns is enzyme stability, particularly under harsh process conditions (e.g., high temperatures, extreme pH, or organic solvents). Enzymes can denature or lose activity outside of their native environments.[89] To address this, protein engineering techniques such as directed evolution and rational design are employed to enhance enzyme robustness and catalytic efficiency. Another challenge is the requirement for cofactors, which are often expensive and must be regenerated in situ for economically viable processes. Cofactor regeneration strategies - such as enzymatic coupling reactions, electrochemical methods, or whole-cell systems - are under active development to address this issue.

Enzyme immobilization is another critical strategy to improve operational stability, reusability, and ease of separation from the reaction medium.[90] Techniques include adsorption on solid supports, covalent

bonding, entrapment in gels, and encapsulation. Immobilization can not only enhance enzyme resistance to denaturation but also allow for continuous processing in flow reactors, thereby improving scalability.

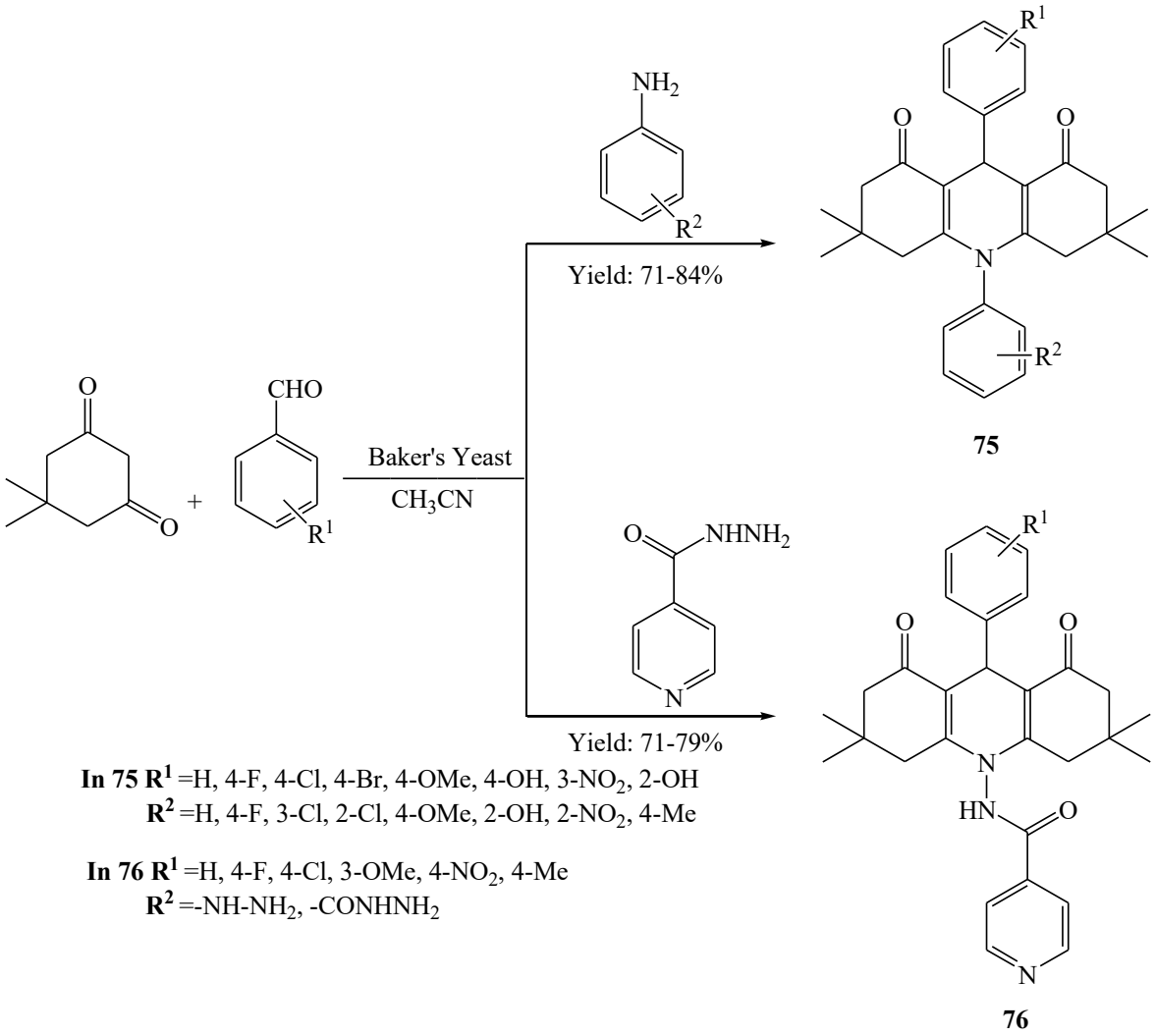
Significant progress has been made in biocatalytic synthesis, especially for nucleoside analog medicines. The synthetic processes of many drugs which are currently in medicinal trials - are mainly biocatalytic. These methods operate efficiently at ambient pressure and temperature, offering substantial benefits over traditional chemical manufacturing by producing superior-quality products with reduced environmental impact.[91-92]

Tyagi and Fasan[93] reported an efficient method for synthesizing ethyl cinnamate **74** (Scheme 58) from benzaldehyde and ethyl α-diazoacetate. The reaction employed the myoglobin variant Mb(F43V,V68F) in combination with triphenylphosphine ($AsPh_3$) as a catalyst, in the occurrence of sodium dithionite and potassium phosphate buffer. The reaction was carried out at room temperature for 12 h, achieving excellent diastereoselectivity and high chemoselectivity.



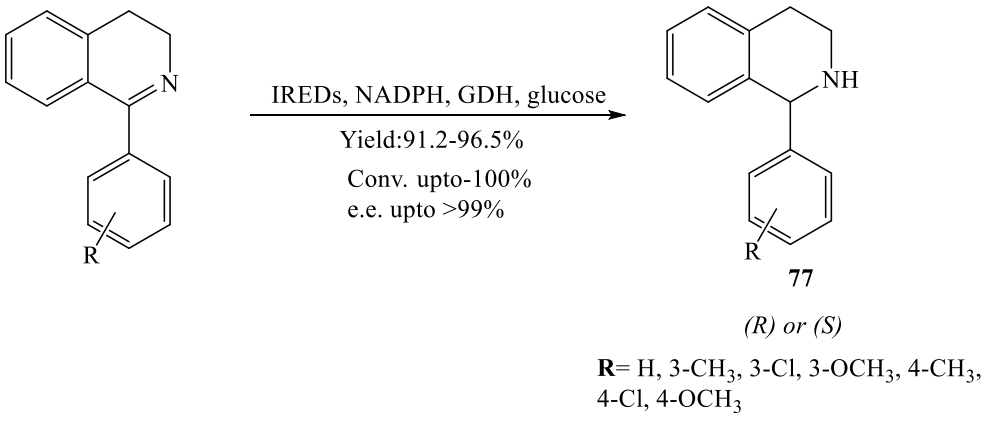
Scheme 58. Synthesis of ethyl cinnamate **74**.

Chate *et al* reported a green process for the synthesis of N-substituted decahydroacridine-1,8-dione derivatives **75** and **76** (Scheme 59) through a multicomponent reaction.[94] In this method they employ Saccharomyces cerevisiae (baker's yeast) as a biocatalyst and utilizes ultrasonication to enhance the reaction efficiency. The chemistry behind this method leverages the catalytic abilities of Saccharomyces cerevisiae, which acts as a source of enzymes - primarily lipases and oxidoreductases - that facilitate key organic transformations such as Michael additions and tandem condensations. The reaction involves dimedone, benzaldehyde, and aniline as starting materials, where the yeast catalyzes the production of the wanted N-substituted compound through a sequence of condensation steps. Ultrasonication enhances the reaction by disrupting yeast cells, allowing faster enzyme release and promoting higher yields in significantly reduced time.



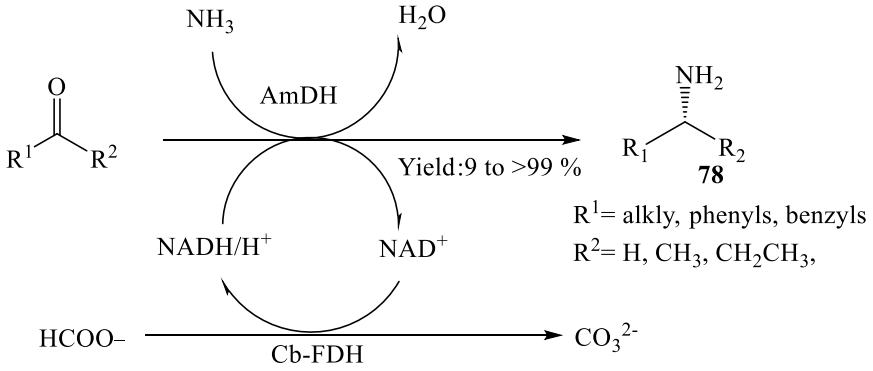
Scheme 59. Synthesis of N-substituted decahydroacridine-1,8-dione derivatives **75** and **76**.

Asymmetric reduction of 1-aryl-dihydroisoquinolines into corresponding 1-aryl-tetrahydroisoquinolines **77** by using an enzyme (Scheme 60), imine reductases (IREDs) in the presence of co-factor glucose dehydrogenase (GDH)/ NADPH has been reported by Zhu *et* al.[95] The method significantly expands the toolbox of IREDs, offering a cost-effective biocatalytic approach for synthesizing compound **77** and setting a foundation for future protein engineering aimed at creating even more versatile and selective enzymes.



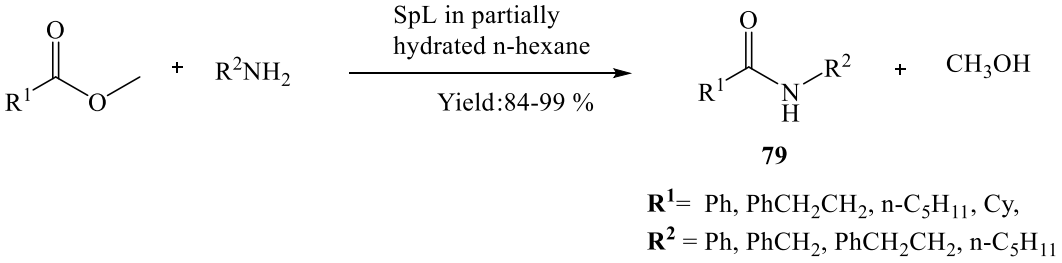
Scheme 60. Synthesis of 1-aryl-tetrahydroisoquinolines **77**.

Knaus *et al*[96] have reported the synthesis of chiral amines **78** *via* reductive amination of ketones or aldehydes catalyzed by an enzyme, amine dehydrogenases (AmDHs) in the presence of coenzyme, formate dehydrogenase from Candida boidinii (Cb-FDH) in ammonium formate buffer system (Scheme 61). In this method, three AmDHs, Bb-PhAmDH (L-phenylalanine dehydrogenase from Bacillus badius), Rs-PhAmDH (L-phenylalanine dehydrogenase from Rhodococcus sp. M4), Ch1-AmDH (chimeric amine dehydrogenase enzyme), were evaluated, each working in tandem with Cb-FDH for NADH recycling. This method has the advantage of no need for expensive or toxic metal catalysts, high atom efficiency (buffer serves dual role as N-source and reductant), avoids high-pressure hydrogen and extensive protection/deprotection steps, simple work-up, and no need for acetone removal.



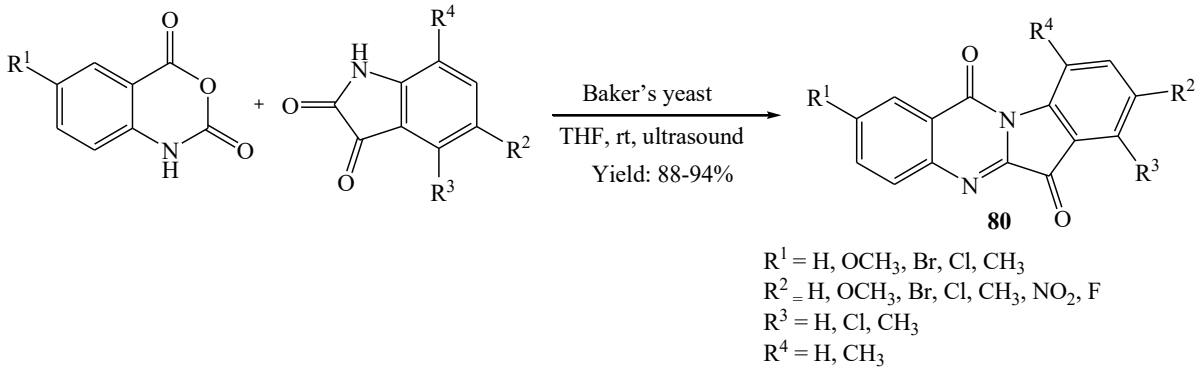
Scheme 61. Synthesis of chiral amines **78**.

Synthesis of amides **79,** by the reaction of esters with amines at 30 °C and 250 rpm stirring in partially hydrated n-hexane in the presence of the enzyme (Scheme 62), intracellular lipase, SpL (Spore Photoproduct Lyase) from *Sphingomonas sp.* HXN-200, has been reported by Zeng *et* al.[97] The unique properties of SpL, such as high activity, broad substrate acceptance, enantioselectivity, and operational simplicity, suggest significant potential for pharmaceutical and fine chemical applications.



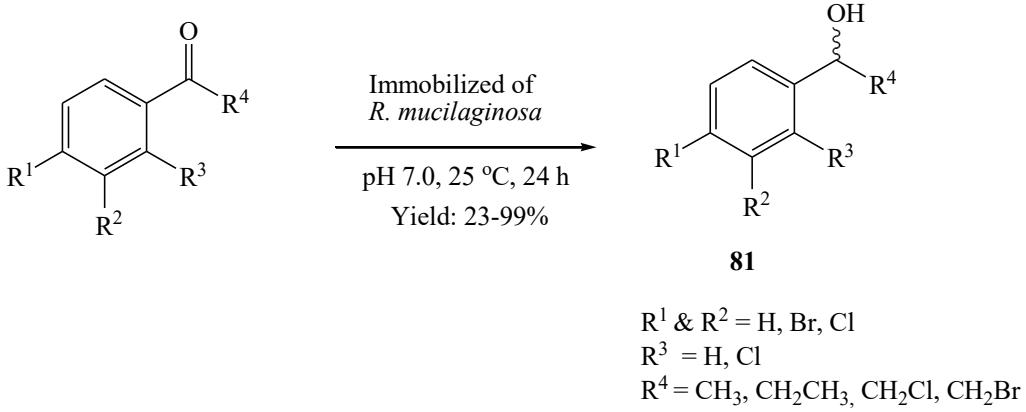
Scheme 62. Synthesis of amides **79**.

Mane *et al.*[98] described the formation of indolo[2,1-*b*]quinazoline-6,12-diones **80** (Scheme 63) through the reaction of isatoic anhydrides with isatins. The reaction was carried out at room temperature under ultrasonic irradiation of frequency, 30 kHz and power, 100 W using baker's yeast and tetrahydrofuran (THF) as the solvent, demonstrating an efficient and green approach.



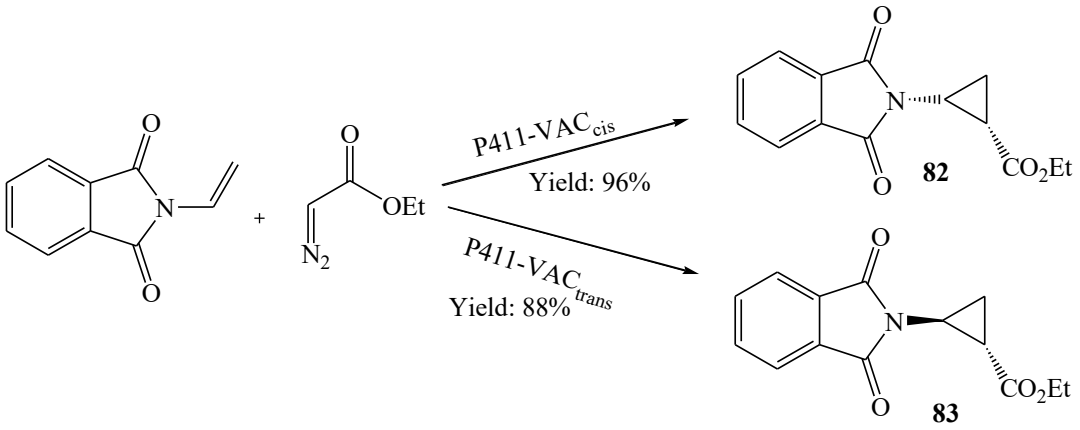
Scheme 63. Synthesis of indolo[2,1-*b*]quinazoline-6,12-diones **80**.

Liu and co-workers[99] described the enantioselective reduction of ketones to the alcohols **81** (Scheme 64) in the presence of Rhodotorula mucilaginosa resting cells or immobilized cells. The cells were immobilized with either agar or a calcium alginate/PVA-alginate matrix. The reaction was performed in the presence of a Na_2HPO_4-KH_2PO_4 buffer (pH 7.0) containing glucose, at 25 °C for 24 hours, achieving high enantioselectivity.



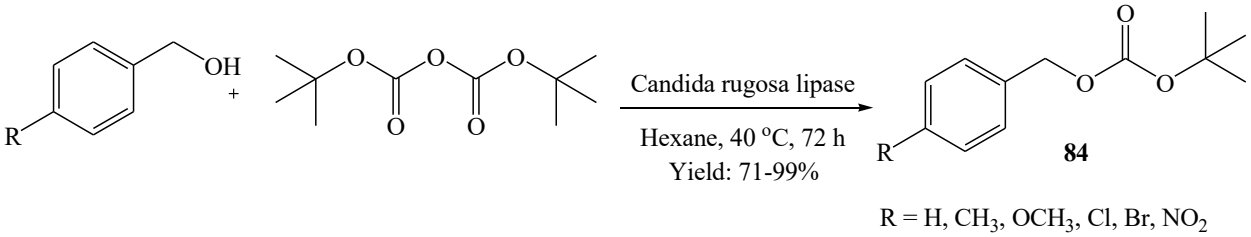
Scheme 64. Synthesis of alcohols **81**.

Brandenberg *et al*.[100] reported the selective cis- and trans-cyclopropanation of N-vinylphthalimide with ethyl diazoacetate (EDA), yielding either ethyl (1S,2S)-2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1-carboxylate **82** or ethyl (1S,2R)-2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1-carboxylate **83** (Scheme 65). The reactions were catalyzed by engineered *E. coli* variants, P411-VACcis or P411-VACtrans, respectively. The process was conducted in a mixture of dimethyl sulfoxide and ethanol, supplemented with M9-N buffer and NADPH. The reaction mixture was shaken at room temperature for 1 to 6 hours to achieve desired products.



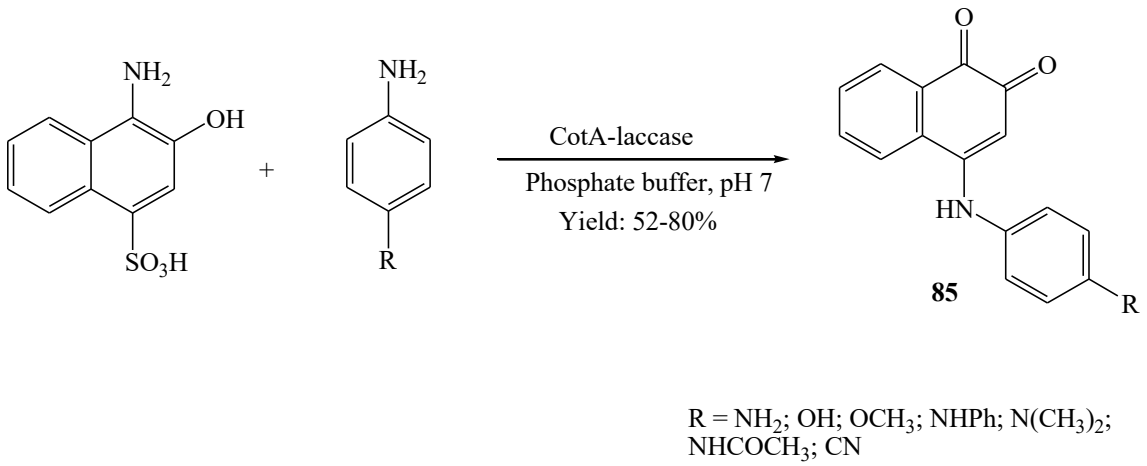
Scheme 65. Synthesis of 2-(1,3-dioxoisoindolin-2-yl)cyclopropane-1-carboxylate **82** and **83**.

Kishi and Kojima[101] reported the tert-butoxycarbonylation of alcohols with di-tert-butyl dicarbonate (BoC_2O) by using biocatalyst, Candida rugosa lipase. The reaction was performed in hexane at 40 °C for 72 h, yielding the corresponding tert-butoxycarbonyl (Boc)-protected alcohols **84** (Scheme 66).

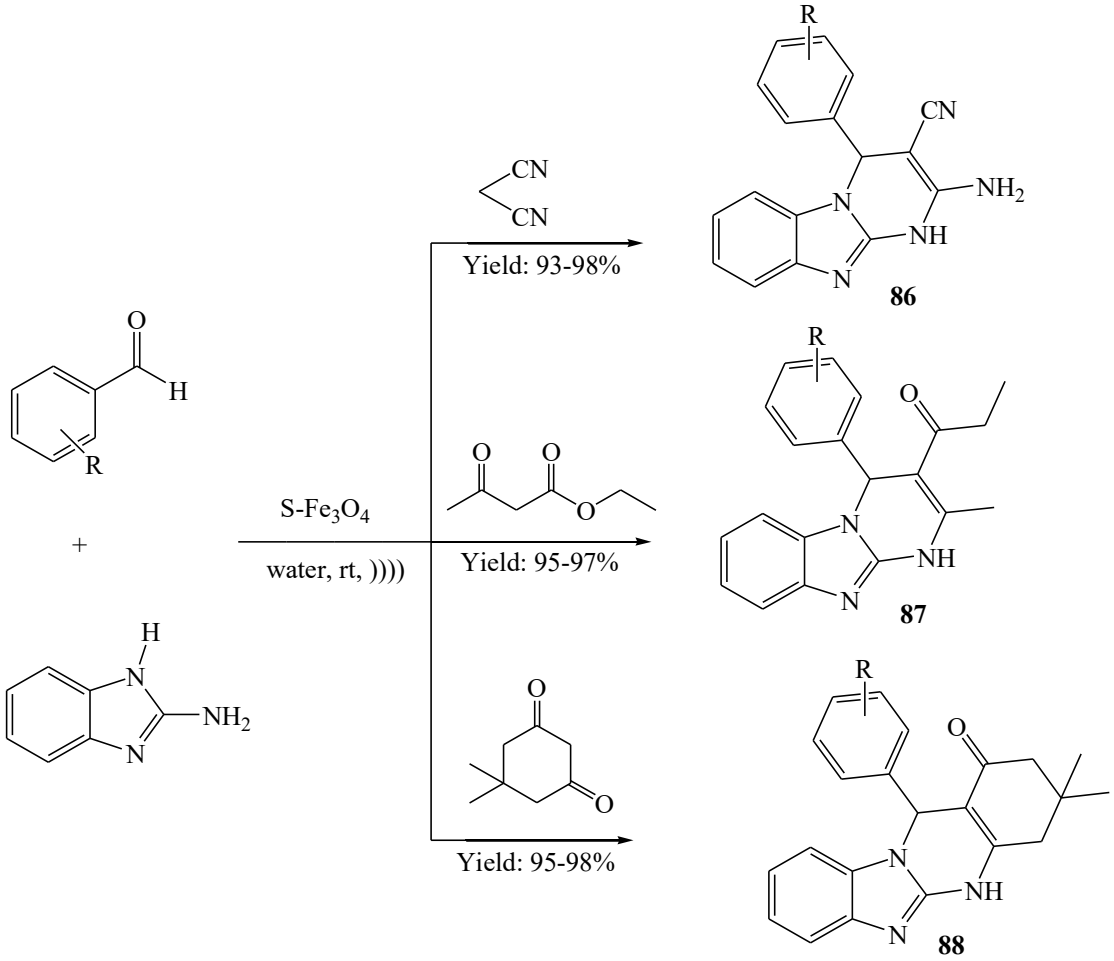


Scheme 66. Synthesis of *tert*-butoxycarbonyl (Boc)-protected alcohols **84**.

The production of 4-arylamine-1,2-naphthoquinones **85** (Scheme 67) utilizing CotA-laccase from Bacillus subtilis by Sousa *et al*. highlights an innovative green chemistry approach.[102] This biocatalytic method circumvents the traditional chemical oxidants and solvents by utilizing an enzyme-mediated cross-coupling reaction. The reaction is conducted in an aqueous medium, utilizing oxygen as a co-substrate, which promotes the nucleophilic attack of substituted aromatic amines on the quinone core. This strategy offers a cleaner, more sustainable alternative to conventional synthesis, yielding the naphthoquinones in 52-80% yield. The electrochemical and kinetic data indicate that CotA-laccase has a strong affinity for AHNSA, favoring its oxidation over other amines, which contributes to the enzyme's selectivity in cross-coupling reactions. This method expands the synthetic applications of CotA-laccase, demonstrating its potential for creating bioactive naphthoquinone derivatives, especially in pharmaceutical chemistry.



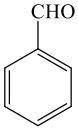
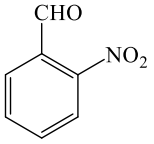
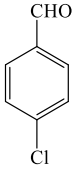
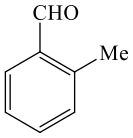
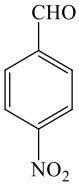
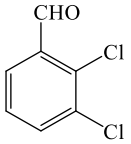
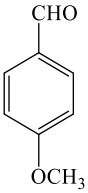
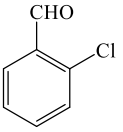
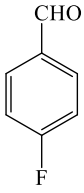
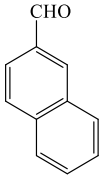
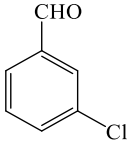
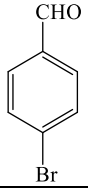
Scheme 67. Synthesis of 4-arylamine-1,2-naphthoquinones **85**.

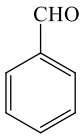
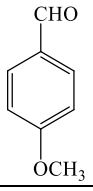
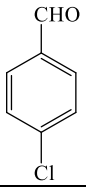
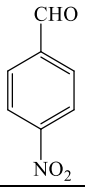


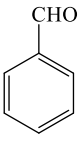
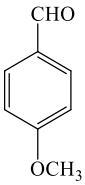
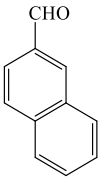
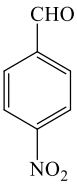
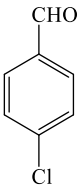
Scheme 68. Synthesis of imidazopyrimidines **86, 87** and **88**.

Verma *et al*. described a method for synthesizing biologically important imidazopyrimidines **86**, **87** and **88** (Scheme 68) employing biocatalyst, starch-functionalized magnetite (s-Fe_3O_4) nanoparticles.[103] The chemistry centers on multicomponent reaction carried out under ultrasound irradiation in water. The starch-

functionalized magnetite nanoparticles enhance the catalytic efficiency by increasing surface area and enabling easier recovery through magnetic separation. The study highlights water as a green solvent, achieving excellent yields (up to 98%) with rapid reaction times. The nanoparticles exhibit good reusability, maintaining catalytic activity for up to six cycles. This green chemistry approach offers a sustainable and efficient alternative for imidazopyrimidine synthesis, addressing environmental and economic concerns through reduced waste, energy, and solvent usage.

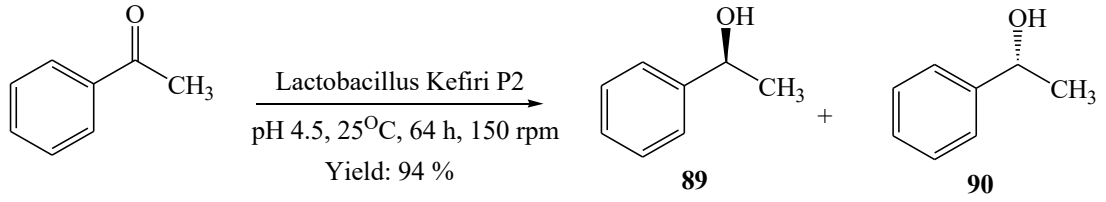
86	**Aldehyde**	**86**	**Aldehyde**	**86**	**Aldehyde**
a		e		i	
b		f		j	
c		g		k	
d		h		l	

87	**a**	**B**	**c**	**d**
Aldehyde				

88	**a**	**b**	**c**	**d**	**e**
Aldehyde					

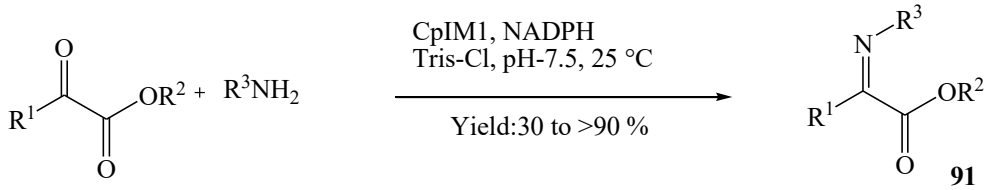
A green synthetic approach using Lactobacillus kefiri P2 as a novel biocatalyst for the production of chiral aromatic alcohols **89** and **90** (Scheme 69) through the bioreduction of various prochiral ketones was developed by Baydas *et al*.[104] The authors systematically optimized key reaction factors like pH, temperature, agitation speed, and reaction time to maximize enantiomeric excess (up to 99%) and conversion rates. The

study highlights the steric and electronic effects of substituents on the aromatic ring, showing that Lactobacillus kefiri P2 exhibited high selectivity depending on the position and nature of these substituents. This green biocatalytic method offers an environmentally friendly and sustainable alternative to traditional chemical methods, with significant potential for industrial applications in producing optically pure molecules. The findings contribute valuable insights into enzyme-based bioreductions, presenting Lactobacillus kefiri P2 as a highly effective biocatalyst for asymmetric reductions in organic chemistry.



Scheme 69. Synthesis of chiral aromatic alcohols **89** and **90**.

Mahesh and Chadha[105] reported a stereospecific imine reductase derived from Candida parapsilosis ATCC 7330 (CpIM1) (Scheme 70). CpIM1 catalyses the alkyl amination of α-keto acids/esters in the presence of NADPH as a cofactor, using a Tris-Cl buffer at pH 7.5–8.5, resulting in the exclusive production of (S)-N-alkyl amino acids/esters **91**, respectively. This is the first report of a purified and characterized imine reductase from yeast, expanding the known toolbox of biocatalysts for chiral amine synthesis. The enzyme shows a preference for substrates with a carboxylic acid group and could potentially be engineered to act on ketones.

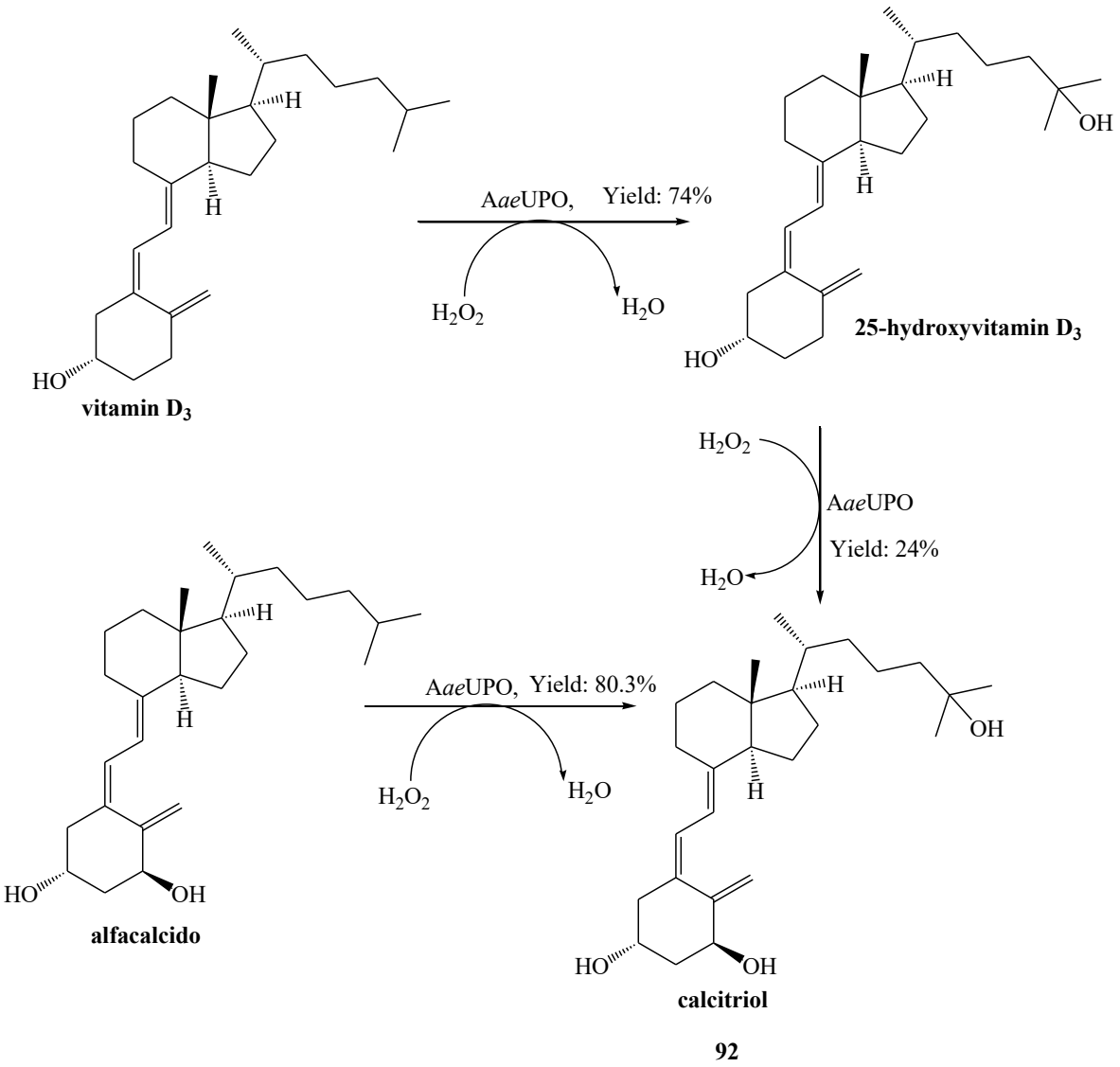


R1= H, Me, Ph, $PhCH_2$, $PhCH_2CH_2$
R2 =H, Et
R3 = H, Me, Et

R1= H, Me, Ph, $PhCH_2$, $PhCH_2CH_2$
R2 = Na, Et
R3 = H, Me, Et

Scheme 70. Synthesis of (S)-N-alkyl amino acids/esters **91.**

The single-step conversion of alfacalcidol into calcitriol **92** by using the catalyst, Peroxygenase from Agrocybe aegerita (AaeUPO), in the presence of H_2O_2 in 8h has been reported by Li *et* al.[106] They have also noted that in the presence of AaeUPO, vitamin D_3 yields 25-hydroxyvitamin D_3 predominantly (74%), with some calcitriol **92** (24%) (Scheme 71). This work demonstrates a new, efficient enzymatic route for producing calcitriol **92** from alfacalcidol, with the potential to also use vitamin D_3 directly. The approach is simpler, selective, and avoids multistep chemical synthesis, suggesting potential for future industrial application.



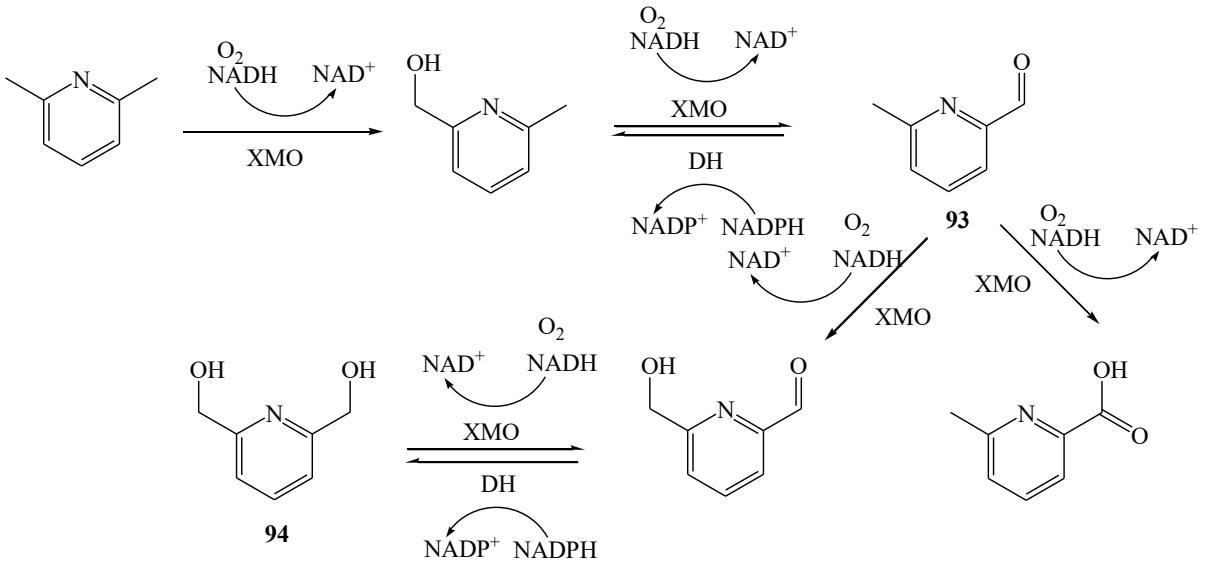
Scheme 71. Synthesis of Calcitriol **92**.

Kardashliev *et al.*[107] developed an innovative biocatalytic process for the synthesis of 2,6-bis(hydroxymethyl)pyridine **94** from 2,6-lutidine. This process utilized recombinant Escherichia coli whole cells engineered to express the enzyme xylene monooxygenase (XMO). This process, characterized as a one-pot synthesis, showcased significant advancements in efficiency. The authors reported that this method offers a more sustainable alternative to traditional multi-step organic syntheses, which often require harsh oxidizing and reducing agents, resulting in lower yields and higher environmental impact.

The biotransformation involves the oxidation of methyl groups in 2,6-lutidine, initially converting it to 6-methyl-2-pyridine methanol **93**, followed by a cascade of reactions mediated by XMO and endogenous *E. coli* enzymes. The study revealed that the biocatalytic system maintains high selectivity and efficiency, producing compound **94** (Scheme 72) predominantly through an enzymatic oxidation pathway that circumvents the limitations associated with synthetic methods. Importantly, this biocatalytic process operates under mild conditions, utilizing aqueous solvents, which minimizes the environmental footprint of the synthesis.

Furthermore, the research highlights challenges such as substrate toxicity, which can inhibit cell growth and enzymatic activity. This issue was addressed by optimizing the feeding strategy of the substrate to prevent

toxic accumulation while maximizing product yield. Overall, the work illustrates the potential of whole-cell biocatalysis in synthesizing valuable chemical intermediates like 2,6-bis(hydroxymethyl)pyridine, emphasizing its contributions to greener chemistry by reducing the reliance on harmful reagents and conditions typically used in traditional chemical synthesis.

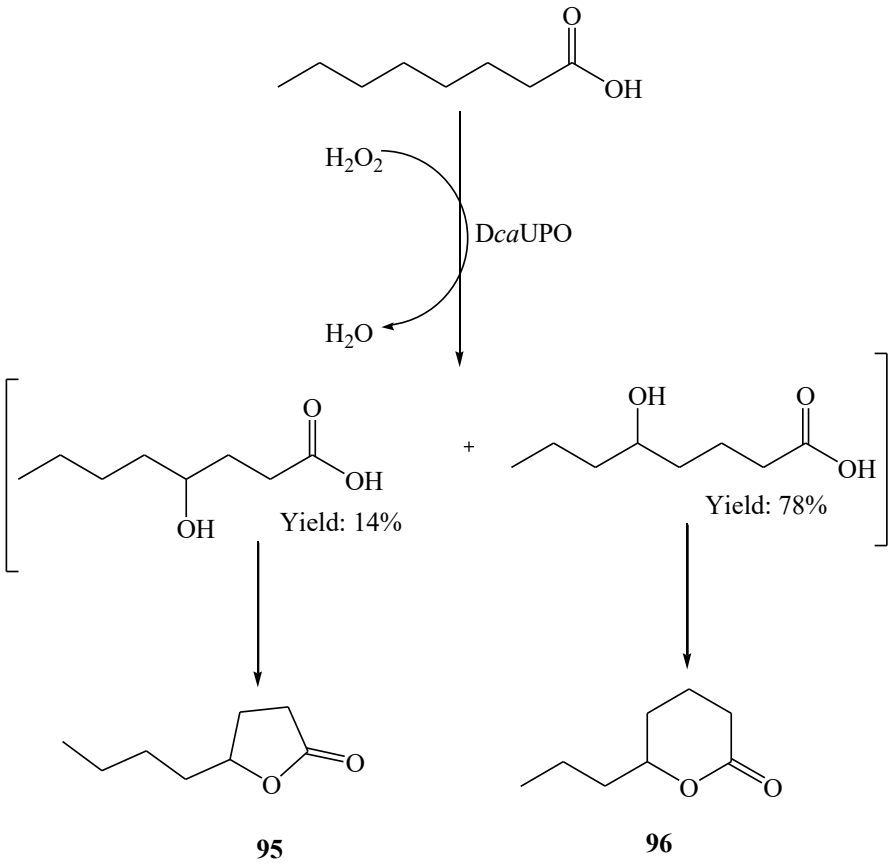


Scheme 72. Synthesis of alcohols **93** and **94**.

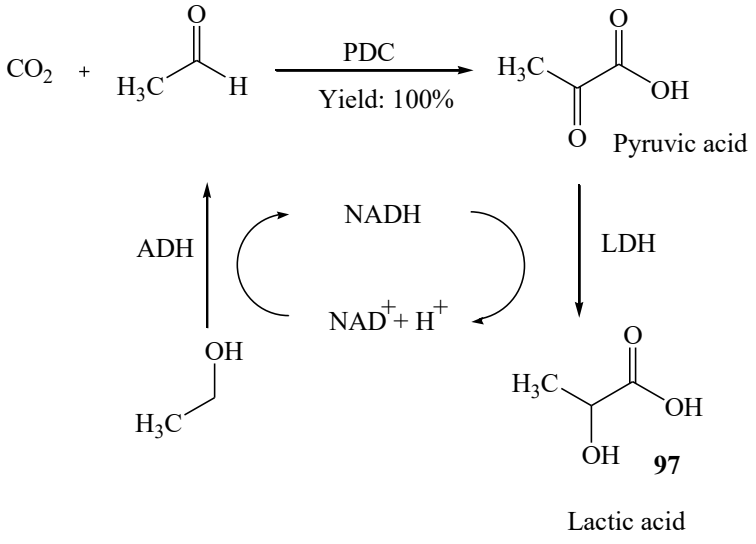
Ebrecht *et al*[108] have reported that unspecific peroxygenases from *Daldinia caldariorum (*DcaUPO), in a mixture consisting of potassium phosphate buffer (pH 7.0), glucose and acetone, selectively hydroxylate the C4 and C5 positions of octanoic acid to yield after lactonization *γ*-octalactones **95** and *δ*-octalactones **96** (Scheme 73). In this method, in addition to DcaUPO, two other unspecific peroxygenases from *Hypoxylon* sp. EC38 (*Hsp*UPO) and *Talaromyces rugulosus* (*Tru*UPO) were also screened for octanoic, Decanoic and Dodecanoic acid, which also selectively hydroxylate the C4 and C5 positions of these acids to yield, after lactonization corresponding *γ*- and *δ*-lactones. To overcome the overoxidation problem of these acids a bienzymatic cascade was developed using alcohol dehydrogenase (ADH) to reduce oxo acids back to hydroxy acids, which then lactonize to lactones.

Carceller *et al*. have developed a carbon capture and utilization (CCU) method for synthesizing lactic acid **97** (Scheme 74) from carbon dioxide (CO_2) through a biocatalytic approach[109]. The process combines enzymatic reactions with chemical transformations to achieve sustainable lactic acid production, minimizing environmental impact. The key chemistry aspect lies in converting CO_2 into a valuable chemical intermediate, addressing issues of CO_2 emissions. By integrating catalysis and green chemistry, the study provides an innovative pathway for the circular carbon economy, enhancing the utility of CO_2 as a feedstock for industrial chemicals.

The research paper discusses a novel biocatalytic process for carbon capture and utilization (CCU), focusing on converting carbon dioxide (CO_2) into lactic acid, an industrially valuable chemical. The key to this approach is using a biocatalyst, combining enzymatic and chemical processes. Specifically, the study employs a two-enzyme system - formate dehydrogenase and lactate dehydrogenase - to first reduce CO_2 into formate, which is then converted into lactic acid. The process showcases a green chemistry route, reducing reliance on fossil fuels while addressing CO_2 emissions, aligning with sustainability goals in industrial chemistry.

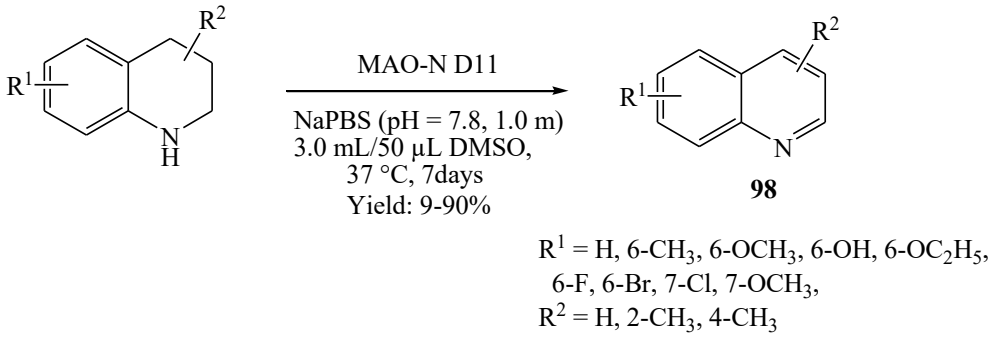


Scheme 73. Synthesis of *γ*-octalactones **95** and *δ*-octalactones **96**.



Scheme 74. Synthesis of lactic acid **97.**

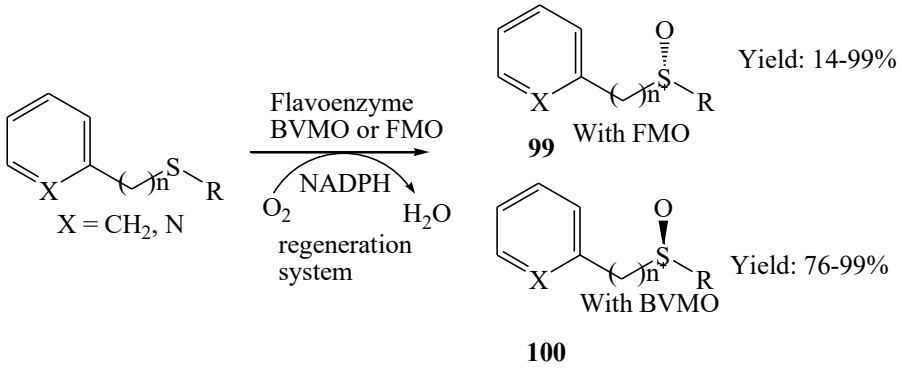
Xiang *et al*[110] have described the conversion of 1,2,3,4-tetrahydroquinolines (THQs) into quinolones **98** (Scheme 75) by biocatalyst Monoamine Oxidase (MAO-N, variant D11) in sodium phosphate-buffered saline (Na_2HPO_4/NaH_2PO_4) at 37 °C for 7 days using DMSO as the cosolvent.



Scheme 75. Synthesis of quinolones **98**.

A research by Wu *et al*. focused on the identification and application of monooxygenase biocatalysts, BVMO145 and FMO401, in the enantiodivergent oxidation of sulfides into sulfoxides **99** and **100** (Scheme 76).[111] The study reveals a significant expansion of the enzymatic toolbox for the selective and environmentally friendly synthesis of optically pure sulfoxides, compounds crucial in pharmaceutical chemistry. BVMO145 selectively produces (S)-sulfoxides **99** with excellent enantiomeric excess (ee) and conversion rates, while FMO401 catalyzes the formation of (R)-sulfoxides **100** with similar efficiency. Importantly, these enzymes provide an eco-friendly alternative to traditional sulfoxidation methods, which typically rely on metal oxidants and chiral ligands. Baeyer–Villiger monooxygenases (BVMOs) and flavin-containing monooxygenases (FMOs), part of the flavoprotein monooxygenases (FPMO) family, demonstrate the potential for sustainable oxidation processes, particularly with sulfur- and nitrogen-containing substrates.

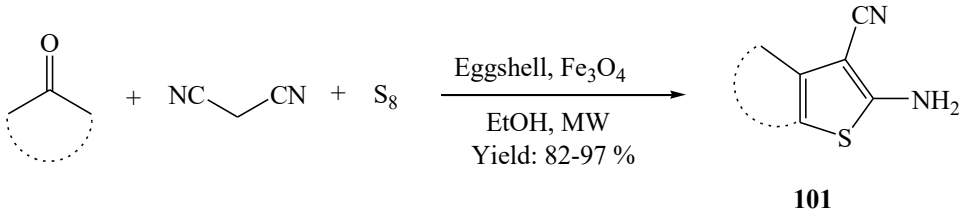
The key findings of the study include BVMO145's high chemoselectivity, which avoids overoxidation and N-oxide by-products, and FMO401's complementary enantioselectivity, offering a versatile approach to asymmetric sulfoxidation. The structural basis for these selectivities was explored through molecular dynamics simulations, revealing how differences in the binding pockets of BVMO145 and FMO401 direct the formation of opposite enantiomers. The active site interactions, particularly the hydrogen bonding and steric hindrance in BVMO145, were identified as crucial factors influencing the stereoselectivity of sulfoxidation. The study not only expands the chemical toolbox for biocatalytic transformations but also highlights the potential for in silico methods to guide future enzyme engineering efforts, offering new avenues for green chemistry applications in drug synthesis and industrial processes.



Scheme 76. Oxidation of sulfides into sulfoxides **99** and **100**.

The synthesis of 2-amino thiophene derivatives **101** (Scheme 77) using a novel biocatalyst composed of Fe_3O_4 nanoparticles impregnated onto eggshells was reported by Zargari *et al*.[112] Eggshell, primarily made of

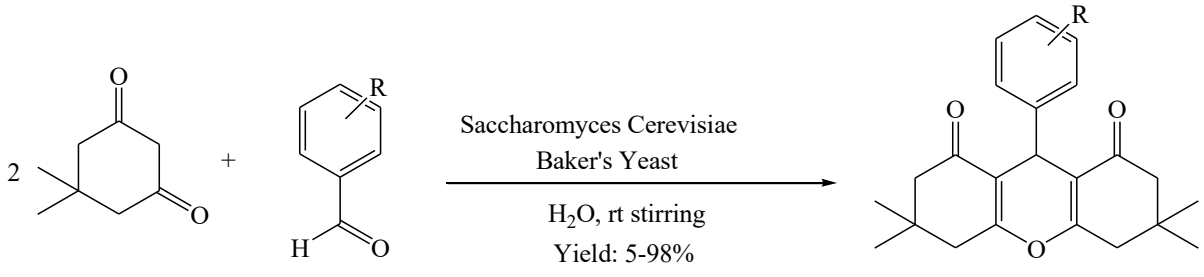
calcium carbonate ($CaCO_3$), was utilized as a cost-effective and biodegradable support for Fe_3O_4 nanoparticles, enhancing its catalytic activity. The catalyst was successfully applied to synthesize thiophene derivatives **101** from aromatic aldehydes, malononitrile, ethyl acetoacetate, and sulfur (S_8), under mild conditions, yielding high product efficiency within 10 minutes under microwave heating in EtOH solvent. The catalytic performance remained stable over five cycles, demonstrating both reusability and sustainability. The study's emphasis on green chemistry and the use of renewable materials, like eggshell, highlights its contribution to environmentally benign chemical processes. Overall, the research effectively integrates materials science and organic synthesis, presenting a viable alternative for the synthesizing valuable heterocycles while minimizing waste and energy consumption.



101

Scheme 77. Synthesis of 2-amino thiophene derivatives **101**.

Hoolageri *et al*. presented a green chemistry approach for synthesizing 1,8-dioxo-octahydroxanthenes **102** (Scheme 78), which are explored as potential HIV reverse transcriptase inhibitors. Using Baker's yeast (Saccharomyces cerevisiae) as a biocatalyst, the authors[113] developed an eco-friendly, cost-effective, and effective method for synthesizing these xanthene derivatives. The reaction involves the condensation of dimedone with aromatic aldehydes, yielding high-purity products with remarkable efficiency (87-96% yield) and minimal byproducts. Docking studies confirmed that these derivatives effectively bind to the active site of HIV-1 reverse transcriptase, with promising inhibitory potential, suggesting their application in anti-HIV drug discovery. This research highlights a sustainable synthetic strategy, merging green chemistry principles with medicinal chemistry applications.



102

Scheme 78. Synthesis 1,8-dioxo-octahydroxanthenes **102**.

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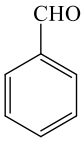
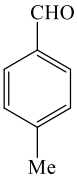
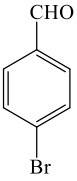
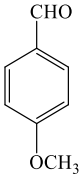
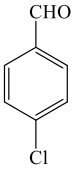
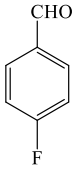
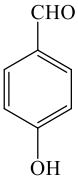
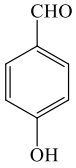
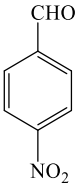
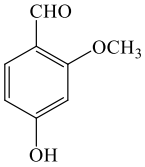
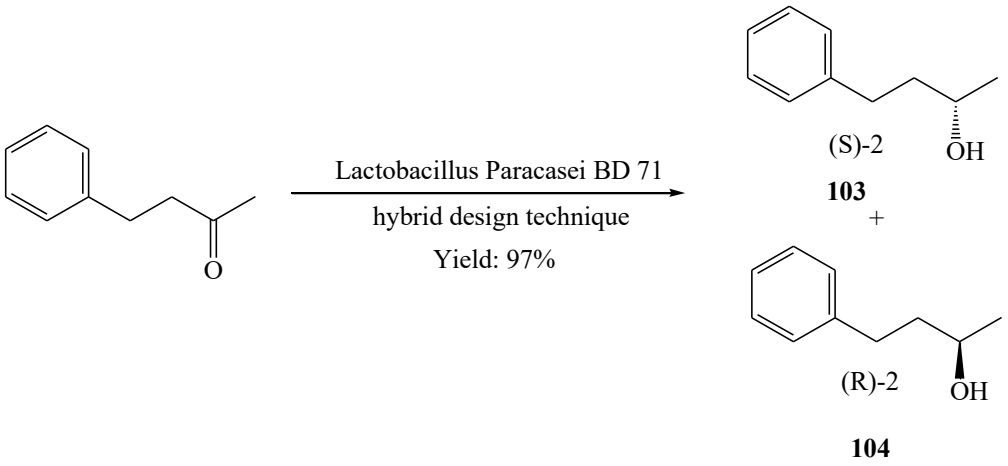
a		F	
b		G	
c		H	
d		I	
e		J	

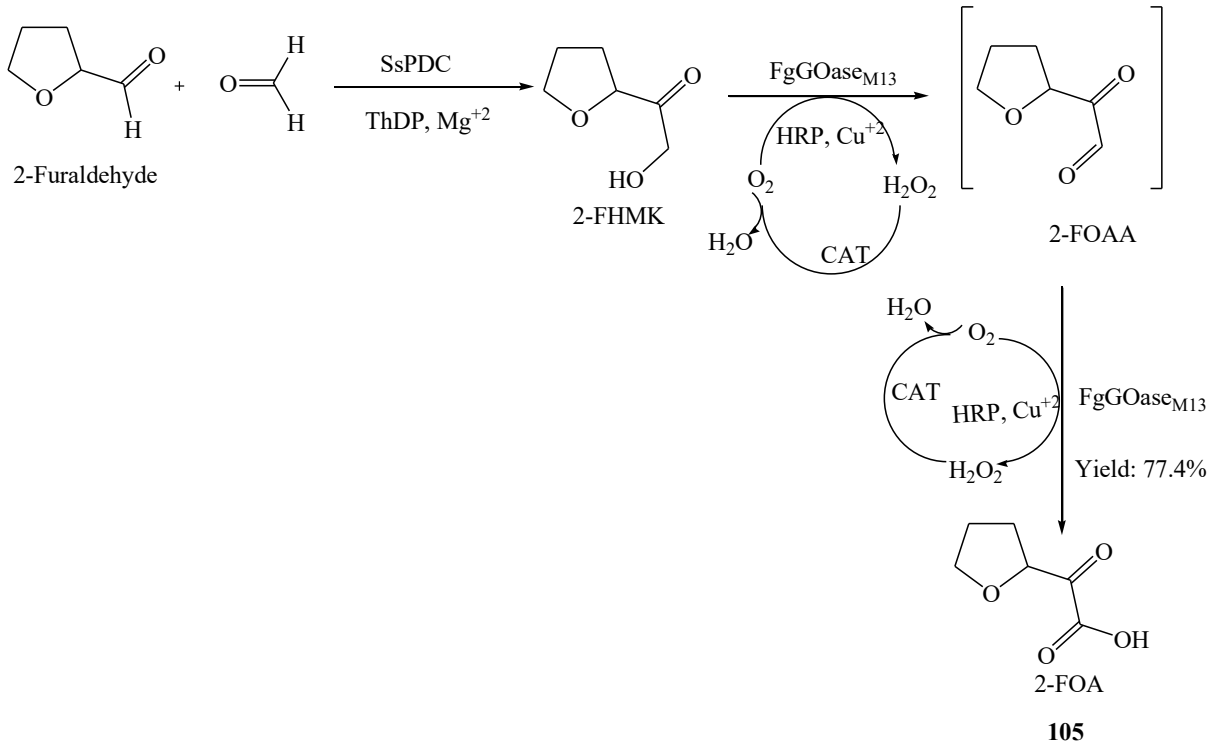
A novel and efficient approach for the bioreduction of 4-phenyl-2-butanone to (S)-4-phenyl-2-butanol **103** and **104** (Scheme 79) was developed by Bayhan *et al*.[114]. The reaction employs Lactobacillus paracasei BD71 as a biocatalyst and introduces a hybrid design-based optimization technique to enhance the reaction's efficiency. Traditional synthetic methods for chiral alcohols often suffer from low optical purity, high cost, and the production of toxic byproducts. In contrast, biocatalytic reduction offers a green alternative, yielding optically pure alcohols under mild conditions.

The paper emphasizes the importance of optimizing bioreduction conditions for optical purity and reaction efficiency, targeting an eco-friendly and scalable method. Using a hybrid design, the researchers optimized key factors such as pH, temperature, incubation period, and agitation speed, achieving optical purity and conversion rates of over 99%. The scale-up experiment demonstrated the feasibility of this approach, successfully converting 14.08 g of 4-phenyl-2-butanone to 13.84 g of (S)-4-phenyl-2-butanol with 97% yield. This marks a significant progress in the biocatalytic production of enantiopure compounds, making the method both industrially applicable and environmentally sustainable.



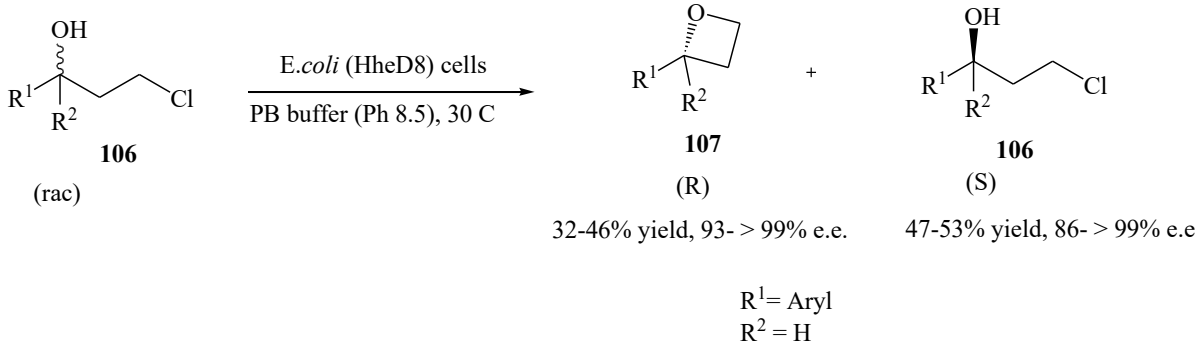
Scheme 79. Bioreduction of 4-phenyl-2-butanone to (S)-4-phenyl-2-butanol **103** and **104**.

Zhang *et al*[115] have reported a two-step bio-catalytic process converting furfural and formaldehyde to 2-(Furan-2-yl)-2-oxoacetic acid (2-FOA) **105** (Scheme 80). In the first step, 2-FHMK (2-furoyl hydroxymethyl ketone) was synthesized from furfural and formaldehyde using SsPDC (a pyruvate decarboxylase from *S. stipitis*). In the second step, 2-FHMK was oxidized to 2-FOA **105** without isolating the intermediate, aldehyde (2-FOAA), in the presence of the M13 mutant enzyme, derived from FgGOase (a copper-dependent galactose oxidase) and the enzyme, horseradish peroxidase (HRP) which functioned as a single-electron oxidant to reactivate FgGOase and Catalase(CAT), which catalyzes the decomposition of hydrogen peroxide into water and oxygen. This method has the advantage of simplified system design, reduced process complexity, minimized waste, and is aligned with green chemistry principles as compared to chemical syntheses of 2-FOA **105**, which involve harsh conditions, toxic reagents, and high waste**,** making them environmentally problematic.

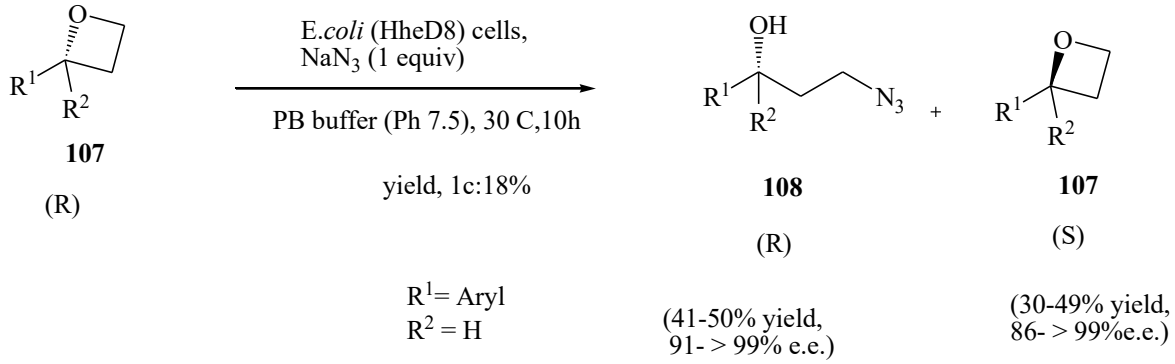


Scheme 80. Synthesis of 2-(Furan-2-yl)-2-oxoacetic acid (2-FOA) **105**.

Hua e*t al*[116] have reported the enantioselective dehalogenation of aryl γ-chloroalcohols **106** to yield both chiral (R)-oxetanes **107** and (S)-aryl-γ-chloroalcohols **106** by applying bio-catalyst, halohydrin dehalogenase from *E.Coli* (HheD8) in PB buffer of Ph 8.5 at 30 °C (Scheme 81). They have also reported enantioselective ring-opening of aromatic substituted (R)-oxetanes **107** *via* treating with sodium azide in the presence of bio-catalyst, HheD8, to yield corresponding chiral (R)-γ-azidoalcohols **108** and (S)-oxetanes **107** (Scheme 82) with good to excellent enantioselectivity. This method is promising for synthetic and pharmaceutical applications, providing greener and scalable routes to valuable chiral molecules.



Scheme 81. Synthesis of chiral (R)-oxetanes 107 and (S)-aryl-γ-chloroalcohols 106.



Scheme 82. Synthesis of chiral (R)-γ-azidoalcohols **108** and (S)-oxetanes **107**.

Industrial scalability of green solvents and biocatalysts

The widespread adoption of green solvents and biocatalysts hinges on their scalability, cost-effectiveness, compatibility with existing infrastructure, and favourable regulatory status. Recent large-scale applications demonstrate their expanding potential beyond laboratory settings.

Green solvents in industry. Green solvents such as supercritical CO_2, bio-based solvents (e.g. ethyl lactate, limonene), and deep eutectic solvents (DESs) have gained traction in various sectors:

• Supercritical CO_2 has been extensively used for decaffeination of coffee, extraction of essential oils, and dry cleaning, offering a non-toxic and recyclable alternative to traditional solvents.

• Bio-based solvents, such as ethyl lactate, are used in pharmaceutical intermediate synthesis and cleaning applications, owing to their low toxicity and biodegradability.

• DESs are now being explored for metal extraction, biomass processing, and enzymatic reactions, with promising pilot-scale studies showing feasibility.

Biocatalysis: commercial success stories. Biocatalysts have already achieved commercial success in multiple large-scale processes due to their high selectivity, mild operating conditions, and reduced need for downstream purification:

• Merck successfully implemented a transaminase-based process for the synthesis of sitagliptin, a diabetes drug, replacing a rhodium-catalyzed route and reducing waste by 19%.

• Novozymes and DSM have commercialized enzyme systems for the production of acrylamide, cellulosic ethanol, and laundry detergents, demonstrating enzyme performance at industrial volumes.

• In the flavors and fragrances industry, lipase- and esterase-catalyzed esterifications are carried out at ton scale for aroma compound synthesis (e.g. isoamyl acetate, ethyl butyrate).

Table 1. Comparative summary of green solvents and biocatalysts

System	Key Properties	Advantages	Limitations
Water	- Polar protic solvent - Non-toxic, abundant, inexpensive	- Environmentally benign - Ideal for many enzymatic and ionic reactions	- Limited solubility for organic compounds - High boiling point - Can hydrolyze sensitive reagents
Ionic Liquids	- Low vapor pressure - Tunable polarity and properties	- Recyclable - Wide electrochemical window - Solubilizes a variety of substrates	- Expensive - Toxicity and biodegradability concerns - Complex purification
PEGs	- Low vapor pressure - Water-miscible (short chains) - Amphiphilic nature	- Biocompatible - Low toxicity - Enhances enzyme stability and selectivity	- High viscosity - Limited solvent power for some non-polar compounds
Biocatalysts	- Enzymes or whole-cell catalysts - Operate under mild conditions	- High selectivity (enantio-, regio-) - Renewable & biodegradable - Minimal side-products	- Sensitivity to temperature/pH - Costly for large scale - Narrow substrate scope in some cases

3. Conclusions

The review highlights the pivotal role of green solvents and biocatalysts in driving sustainable chemical synthesis, showcasing their potential to replace traditional methods that often involve hazardous chemicals and energy-intensive processes. Water, with its abundant availability and eco-friendliness, stands as a model green solvent, particularly in aqueous phase reactions. Ionic liquids, known for their tunable properties, have demonstrated versatility and efficiency across various synthetic pathways while minimizing environmental impact. Similarly, polyethylene glycol (PEG) emerges as an effective and biodegradable solvent, further extending the scope of green chemistry. Complementing these solvents, biocatalysts provide an innovative and sustainable means to achieve high-yield and selective chemical transformations under mild conditions.

Together, these technologies align perfectly with green chemistry principles, emphasizing reduced toxicity, energy efficiency as well as resource conservation.

4. Future Scope

The field of green solvents and biocatalysis is rapidly evolving, with several cutting-edge trends offering promising solutions to current challenges and unlocking new opportunities for sustainable synthesis:

1. Optimization of Green Solvents. Beyond ionic liquids and PEGs, deep eutectic solvents (DESs) are emerging as attractive, biodegradable, and tunable alternatives. Their ease of preparation, low cost, and wide applicability in catalysis and biotransformations position them as next-generation green solvents. Future work should focus on task-specific DESs designed for selectivity, recyclability, and process compatibility.

2. AI-Driven Biocatalyst Design and Integration. The integration of artificial intelligence (AI) and machine learning (ML) is revolutionizing enzyme engineering. Predictive models can now analyze large datasets to forecast enzyme activity, stability, and substrate compatibility, significantly reducing development time. Coupling AI with directed evolution and high-throughput screening will enable the rapid discovery of bespoke biocatalysts tailored to industrial needs.

3. Solvent-Biocatalyst Synergy in Smart Systems. Future research should emphasize synergistic reaction systems that combine biocatalysts with novel green solvents (e.g, DESs, supercritical fluids, bio-based solvents). These integrated systems could enable one-pot cascade reactions, in situ product removal, and improved mass transfer, thereby enhancing reaction efficiency and sustainability.

4. Economic and Process Feasibility through Innovation. Advancements in enzyme immobilization techniques, such as 3D-printed biocatalytic supports and smart polymers, can enhance enzyme reusability and process scalability. Likewise, continuous-flow biocatalysis using green solvents offers economic benefits through reduced waste and improved throughput.

5. Broadening Applications via Interdisciplinary Approaches. The expanding role of green solvents and biocatalysts in biomass valorization, CO_2 utilization, pharmaceutical manufacturing, and polymer synthesis underscores their versatility. Emerging hybrid systems combining biocatalysis with photocatalysis or electrochemistry are poised to unlock entirely new synthetic pathways with unprecedented selectivity and efficiency.

In conclusion, the convergence of novel green solvent systems, AI-assisted biocatalyst development, and process intensification strategies is setting the stage for a transformative shift in sustainable chemical manufacturing. These innovations promise not only to minimize the environmental footprint of synthesis but also to reshape the future of green chemistry across diverse industrial sectors.

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