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Micelle-driven organic synthesis: an update on the synthesis of heterocycles and natural products in aqueous medium over the last decade

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Organic synthesis guided by micellar nanoreactors constitutes one of the fundamental fields of organic chemistry that is expected to furnish chemical synthesis in a sustainable fashion. Due to its promise, we were also attracted to using the micelles to enhance chemical reactivity and selectivity and to explore their newer applications in natural products and heterocyclic chemistry. As on date, there is no comprehensive review article that highlights the repertoire of chemical reactions developed in micelles furnishing a range heterocycles and natural products/scaffolds, barring the metal-catalyzed cross-coupling reactions. In this review, we document the last decade (2014–2024) progress of organic reactions developed in micelles to yield a range of heterocyclic and natural product-based scaffolds. Notably, we have excluded the content related to metal-catalyzed cross-coupling reactions and some other aspects of micelles due to the number of overlapping reviews written on such topics. In the current article, we briefly introduce micellar catalysis, regions of reaction sites in micelles, and various surfactants utilized in micelle chemistry. Our discussion also captures the importance of micellar catalysis compared to the conventional organic synthesis. More importantly, the focus of our review is largely on the collection of chemical transformations accomplished in the last decade in accessing heterocycles and natural products to showcase the advancement of organic synthesis through sustainable fashion. Wherever required, we have also captured the various interactions of surfactants with the substrates necessary for driving the reactions and discussed the importance of these heterocycles/natural products in intercepting the key biological pathways.

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1 Introduction

Micelles represent the aggregation of surfactant molecules in a liquid, particularly in water. A typical micellar structure in water has its “hydrophilic head” in contact with the water and its “hydrophobic tail” positioned inside the assembly, resulting in the formation of dynamic nano-aggregates of various shapes and sizes.¹ Often these aggregates are spherical, but shapes like ellipsoids, cylinders, and bilayers are also known. The molecular geometry of surfactant molecules, their concentration and certain environmental factors like pH, temperature and ionic strength determine the structure of micellar assemblies.² Overall, a micellar system is a microheterogeneous two-phase colloidal system and appears homogeneous due to the colloidal size of these aggregates.³ Aggregation of surfactant molecules occur only when their concentration is at or above the critical micelle concentration (CMC) and the temperature is equal or above the Krafft temperature. During the formation of

micellar assemblies, hydrophobic interactions are believed to be the driving force for their formations. These hydrophobic effects are attributed to the structural competition between the hydrogen bondings of interfacial and bulk water.⁴

The structure of a normal micelle harbors a hydrophilic outer region-the stern layer, the inner hollow part encircled by hydrophobic tails is called the core, and the hydrophobic tail-containing area between the core and stern layer is called the palisade region (Fig. 1). The hydrophobic tails of the reverse micelle are pointing outward, and the hydrophilic heads surround the core. These different regions of the micellar nanoreactors with different environments (compartmentalization effect) act as the reaction pockets for various chemical transformations reminiscent of enzymatic catalysis in nature.⁵

The formation of micelles and their typical morphology are affected by the surfactant concentration, temperature, nature of surfactant and pH of the solution. Change of micellar morphology has been observed from the spherical to rod-shaped through the globular transition state on increasing the concentration of surfactant molecules.⁶ The CMC of micelles is also dependent on temperature (and the Krafft temperature or Krafft point is the temperature at which concentration of surfactants reaches CMC). The other factor affecting the

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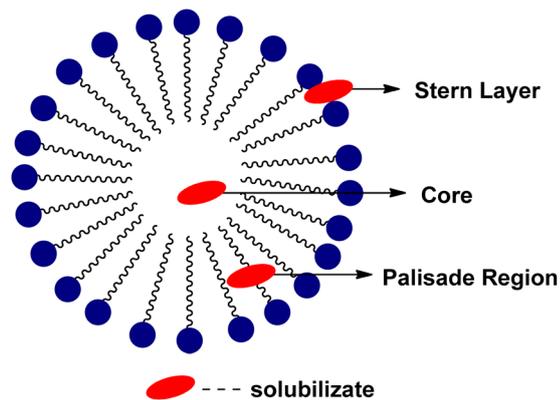


Fig. 1 Structure of normal spherical micelle and its various regions.

micellization is the chain length of amphiphilic molecules which should usually be greater than ten carbon atoms. In a typical micelle, generally 50–100 surfactant molecules are present which are in thermodynamic equilibrium having an average lifetime of 10^{-3} – 10^{-2} seconds.⁷

1.1. Determination of size, structure and micellar interactions

For any organic chemistry transformations, the most crucial information required is to know the CMC, size and morphology of micelle-aggregates. Numerous approaches that are all based on the drastic change in the properties of the solution upon passing the critical micelle concentration. The most widely used techniques for calculating the CMC rely on surface tension measurements, conductometry, scattering of light, light absorbance, UV-vis or fluorescence analysis. NMR spectroscopy and several other techniques, including the recently developed smart phone based measurements, are also employed to measure the CMC.⁸ The average size of micellar assemblies are established by the dynamic light scattering (DLS) analysis, which gives information about the hydrodynamic radius of micellar aggregates. DLS also gives the information about the distribution of different micellar structures which are present in a given solution.⁹ Further, the techniques like SEM and TEM analysis help to determine the morphological features and internal structure of micelles in order to establish the actual pictures of the micellar aggregates formed by surfactants.¹⁰

One of the crucial parameters in micelle-guided organic synthesis is to know the interactions between the solubilizates and micellar aggregates. Several groups have utilized NMR techniques (1D and 2D) to establish such interactions. The diffusion coefficient of micellar assemblies determined by means of pulsed field gradient diffusion NMR or DOSY compared to the value of the free solute helps in determining the interaction between the micelles and solubilizates. 2D-NMR experiments like NOESY and/or ROESY have been employed to know the site of surfactant interaction with the solute molecules.¹¹ In an alternative method, the interactions are also established between the solute and assembled surfactants by studying the variation of the chemical shift in the various

protons of surfactant by increasing the concentration of solute molecules. At higher solubilizate concentrations, sometimes the change in NMR peak shape and resolution is also observed.¹²

1.2. Classification of surfactants

Depending upon the charge of the hydrophilic part, surfactants have been categorized into four main types.¹³ Cationic surfactants have positively charged hydrophilic (water-attracting) head. Cetyltrimethylammonium bromide (CTAB, 1), cetylpyridinium bromide (CPB, 2), dodecyltrimethylammonium chloride (DTAC, 3), (–)-*N*-dodecyl-*N*-methylephedrinium bromide (DMEB, 4) *etc.* are typical examples of cationic surfactants (Fig. 2). Anionic surfactants are distinguished by their negatively charged hydrophilic (water-attracting) head. An anionic surfactant's hydrophilic head typically contains a negatively charged group such as sulfate (SO_4), sulfonate (SO_3), or carboxylate (CO_2^-). Sodium dodecylsulfate (SDS, 5), sodium dodecylsulfonate (SDSO_3Na , 6), sodium dodecylbenzenesulfate (SDBS, 7), *etc.* are some of the typical examples of anionic surfactants. Amphiphiles containing both negative and positive charges separated by a spacer are called zwitterionic surfactants. A typical example of zwitterionic surfactant is (3-(1-dodecyl-1*H*-imidazole-3-ium-3-yl) propane-1-sulfonate) (8) in which the changes in the primary structure on head, tail or spacer region can improve the effectiveness of the surfactants. Nonionic surfactants function effectively as emulsifiers, foaming agents, and wetting agents because of their uncharged hydrophilic and hydrophobic groups. The hydrophilic component of nonionic surfactant is primarily composed of poly(ethylene oxide). Brij-30, Brij-35, Brij-58, Triton X-100 and Tween 40 (9–12) are typical examples of this class of surfactants. Recently, some designer amphiphiles derived from vitamin-E and proline, such as TPGS-750-M (13) and PS-750-M (14) respectively and Tween 40 (15) also harbor poly(ethylene oxide) as an integral part of the surfactant.¹⁴ Amphiphilic molecules exhibiting biological functions have also been found in certain groups of bio-surfactants. Among the representative examples are glycolipids (like mannosylerythritol lipids, 16), lipopeptides, phospholipids, fatty acids, neutral lipids and plant-derived saponins (17). The majority of these surfactants are either anionic or neutral, with the hydrophilic portion based on carbohydrates, amino acids, cyclic peptides, phosphates, carboxylic acids, or alcohols, and the hydrophobic part based on long-chain fatty acids, hydroxy fatty acids, or α -alkyl- β -hydroxy fatty acids. These biodegradable surfactants find interesting biological and environmental applications.¹⁵

2 Application of micelles in organic synthesis

During recent times, micelles have gained a considerable attention in food, medicine, beverages, cosmetics, oil refining, environment and material sciences.^{18–27} In chemistry, they provide an alternative way for organic chemists to perform organic reaction in nature's solvent, water, and thereby open an



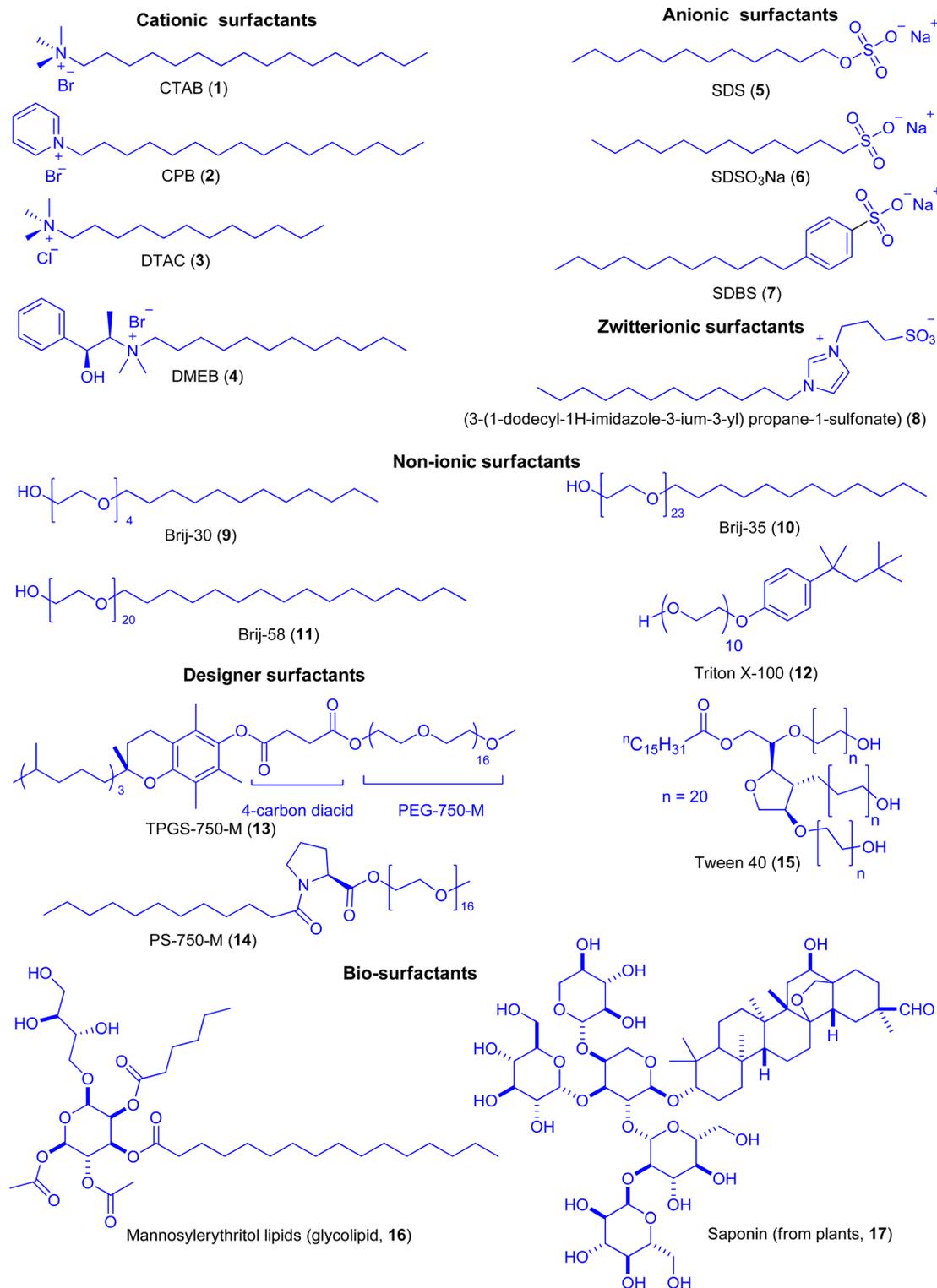


Fig. 2 Structure of various types of commercial, designer and bio-surfactants.

entry towards sustainable organic synthesis. For chemists, water was not an option, since historically, the notion that like dissolves like implies that dissolution is a pre-condition for chemical reactions to take place. Because organic substrates are usually insoluble in water, using water as a solvent has proven

difficult for organic chemists. Due to the poor solubility and low reactivity of reaction partners in water, chemists did not find this option attractive and therefore embraced the organic solvents firmly. Every reaction driven by organic solvents leaves a footprint on our environment and is not a sustainable option



for times to come. For efficient synthesis, selectivity- regio-, chemo- and stereoselectivity is also a major challenge for organic chemists to overcome in the future. Due to the homogeneity, reactions carried out in organic solvents attain evenly distribution of reaction partners and thereby often lead to non-selective products. Using micelles for organic transformation is like mimicking chemical reactions occurring in nature, wherein enzymatic catalysis also involve the hydrophobic and hydrophilic regions as part of the molecular structure.¹⁶ Micelles in aqueous medium are currently used not only as catalysts, but also as solvent mimics and reaction promoters in numerous chemical transformations which has been beautifully captured in a recently published review from Sachin Handa's group.¹⁷ Micelles are known to encapsulate organic substrates, improving solubility, and increasing the local concentration and reactivity of reactants as depicted in Fig. 3.¹⁸ Micelles enhance the reaction selectivity by three main effects: (a) dipoles at water/micellar lipophilic core enhance the regioselectivity; (b) formation of a specific product occurs by substrate/micellar interactions and (c) product selectivity by compartmentalization effect in various micellar regions.¹⁹ Due to these reasons, the use of micelles in synthetic organic chemistry has grown in prominence especially in the last two decades and has been employed in a number of organic transformations. F. Gallou,²⁰ S. Handa,¹⁷ Krause,²¹ and, most importantly, B. H. Lipshutz²² have done ground-breaking work in this area. As a result, many researchers worldwide have reviewed this field's progress from time to time.^{16,17,19,23–28} In our group, we have also attempted to utilize these micellar nano-reactors to induce transformations with enhanced chemical reactivity^{29,30} and selectivity.³¹ The various organic transformations that have been implemented in aqueous micellar catalysis include C–C and C-heteroatom bond formation especially through metal-catalyzed cross-coupling reactions. Further progress in this area was achieved in natural products,²⁴ asymmetric synthesis,³² rearrangement reactions,³³ oxidations/reductions⁴⁸ and heterocyclic synthesis.³⁴ In this review, we aim to chronicle the research accomplishments obtained in the last decade (2014–2024) using micellar catalysis. Our main motif is to cover the synthesis of heterocyclic compounds and natural products which have been accessed in aqueous micellar catalysis to highlight the potential of this area towards sustainable organic synthesis. The purpose is to

stimulate the newer generation of chemists and to encourage them to use water as a solvent in organic synthesis for the longevity of the field of organic synthesis. An enantioselective chemoenzymatic synthesis of the antidementia drug (*S*)-rivastigmine using micellar catalysis by the Lipshutz group has sparked further interest among medicinal chemists in making drugs and natural products using micellar catalysis.³⁵ Developments of newer methods in aqueous medium for the molecules of medicinal and material importance are expected to change the direction of the field of organic synthesis completely. Keeping in mind these aspects, we will discuss in detail the synthesis, micellar-solubilize interactions and biological importance of heterocyclic compounds and natural products (wherever reported) that have been synthesized using micellar catalysis in the last decade. Due to the overlap and to keep the review focused, heterocyclic compounds and natural products synthesis involving metal-catalyzed (especially Pd-catalyzed) cross-coupling reactions have been excluded from this review and appropriate citations have been already covered (*vide supra*).

2.1. Micellar-catalysis in heterocyclic synthesis

A large number of heterocyclic compounds have been synthesized using micellar catalysis. A repertoire of reactions involving carbon–carbon and carbon–heteroatom bond formation reactions, multicomponent reactions, oxidations/reductions, cycloadditions and rearrangement reactions have been established to access various heterocyclic compounds. These transformations reported during the preceding decade have been discussed in the chronological order below:

2.1.1. Synthesis of benzo[*a*]phenazines and naphtho[2,3-*d*]imidazoles.

An expeditious, regio- and chemo-selective synthesis of benzo[*a*]phenazines (**20**) and naphtho[2,3-*d*]imidazoles (**22**) has been established from 2,3-dichloro-1,4-naphthoquinone (**18**) and 1,2-diaminobenzenes (**19**) in water.³⁶ Potassium carbonate in an SDS-micellar medium was highly effective in inducing this transformation into polycyclic heterocyclic with excellent yields, up to 96%. Formation of benzo[*a*]phenazines involves the nucleophilic substitution reaction of the compound **18** and **19** to intermediate **20-I** followed by a second cyclization to **20-II** and its subsequent elimination lead to product **20**, Scheme 1. Similar chemistry was adopted to access the naphtho[2,3-*d*]imidazoles (**22**) by

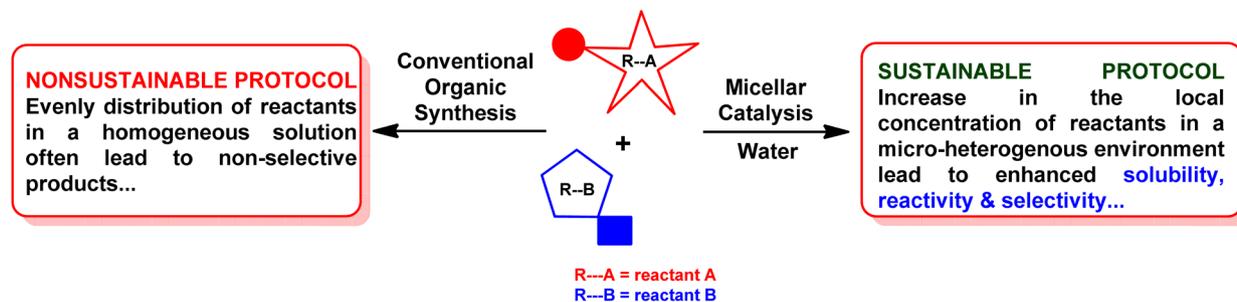
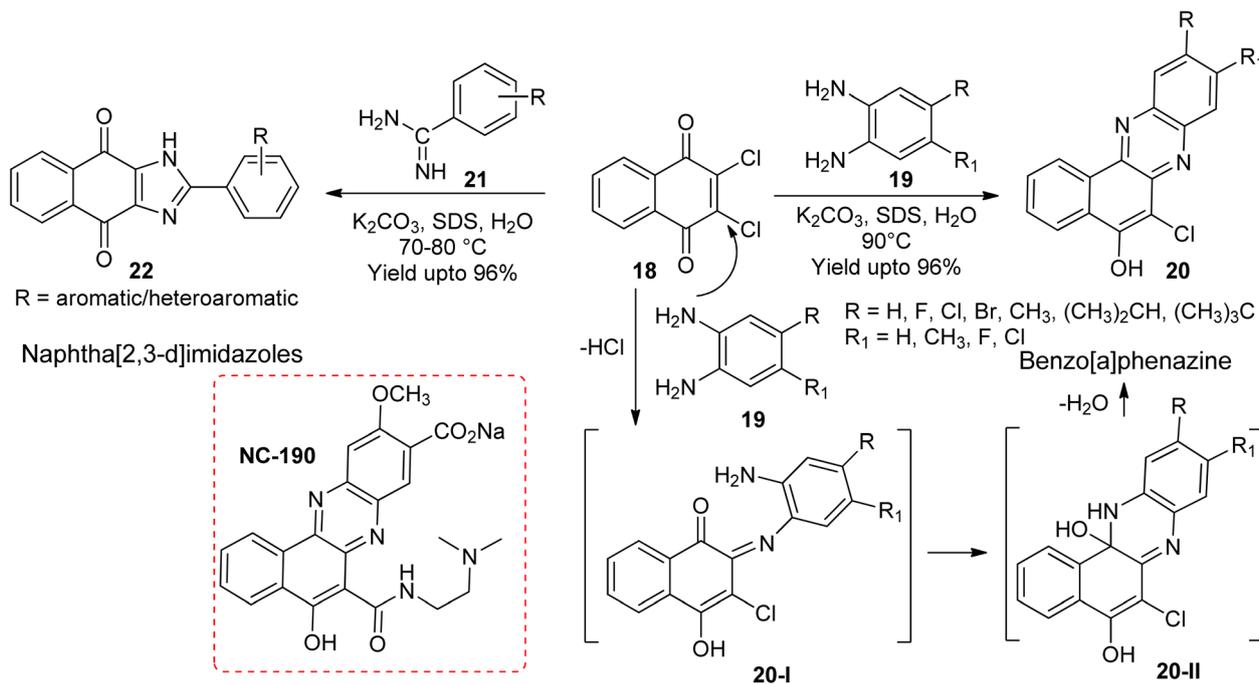


Fig. 3 Diagrammatic representation of reactions in aqueous micelles and in conventional organic solvents.





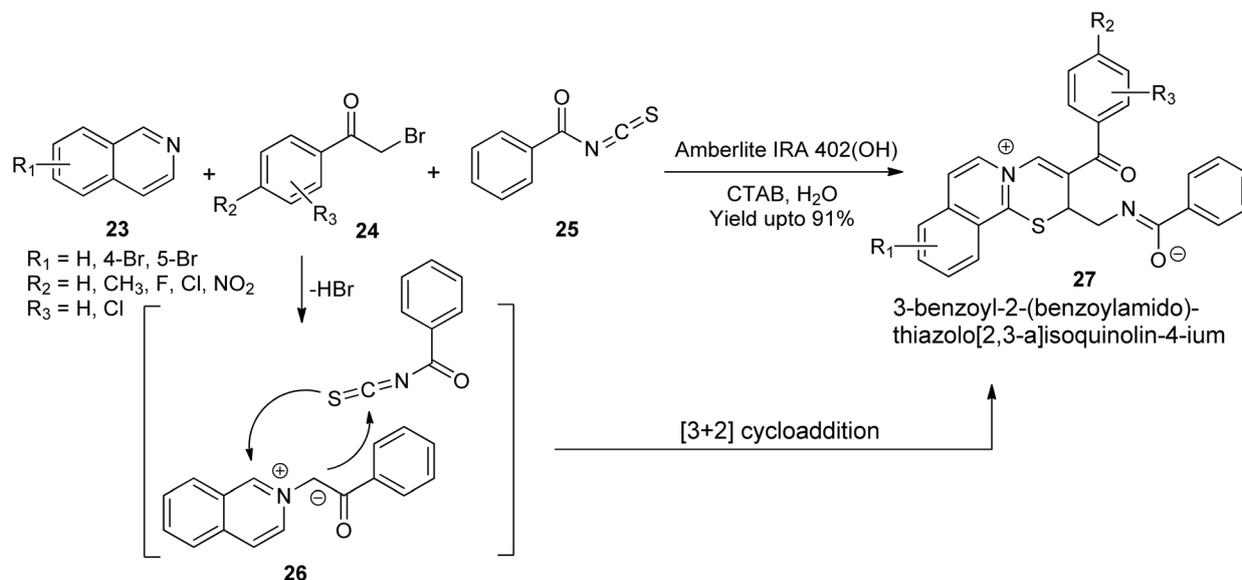
Scheme 1 Synthesis of benzo[a]phenazine and naphtho[2,3-d]imidazoles in aqueous SDS-micellar medium.

reacting compounds **21** with **18**. Further structural diversifications lead to a battery of heterocycles related to an antitumor agent **NC-190**.³⁷

2.1.2. Synthesis of mesoionic thiazolo[2,3-a]isoquinolinium compounds. A one-pot, three-component protocol has been developed for the synthesis of thiazolo[2,3-a]isoquinolinium derivatives (**27**) from isoquinolines (**23**), 2-bromoacetophenone (**24**) and benzoyl isothiocyanate (**25**) in an aqueous cationic micellar medium,³⁸ Scheme 2. In the CTAB micellar assemblies, Amberlite IRA-402(OH)-mediated

generation of isoquinolinium ylide, **26** (generated *in situ* from isoquinoline and phenacyl bromide) adds to activated dienophile (benzoyl isothiocyanate, **25**) through a [3 + 2] cycloaddition reaction to furnish the mesoionic thiazolo[2,3-a]isoquinolinium compounds in excellent yields. These mesoionic compounds have remained the center of attraction to chemists because of the delocalization of positive and negative charges and their associated unusual properties.

2.1.3. Synthesis of chromeno[2,3-b]quinolinediones. In a three-component protocol, reaction between the chromene-3-



Scheme 2 Synthesis of mesoionic thiazolo[2,3-a]isoquinolinium compounds in CTAB-micellar medium.



carbaldehyde (**28**) aromatic amine (**29**) and dimedone (**30**) furnished the 5-aryl-3,3-dimethyl-2,3-dihydro-5aH-chromeno[2,3-*b*]quinoline-1,11-(4*H*, 5*H*)-dione (**31**) in aqueous micellar conditions and in quantitative yields,³⁹ Scheme 3. The reaction operates through the formation of Schiff base (**31-I**) between the **28** and **29** followed by the 1,4-addition of **30** and cyclization through **31-I** and **31-II** to pyran ring construct **31-III**. Structural reorganization of the intermediate **31-II** and elimination of water yielded the desired product **31** in excellent yield. Authors have also carried out a comparative analysis of this methodology in conventional organic solvents and found that the yield and reaction time of the micelle-mediated operations are better than in organic solvents and deemed it an appropriate method for the production of the chromeno[2,3-*b*]quinolinedione heterocyclic compounds.

In its other variant, Manisha R. Bhosle *et al.* have developed an efficient multicomponent synthesis coumarin-fused thiazolyl chromeno[4,3-*b*]quinolines from the corresponding aldehydes, amines, 1,3-cycloalkdiones and coumarins in CTAB micellar medium.⁴⁰

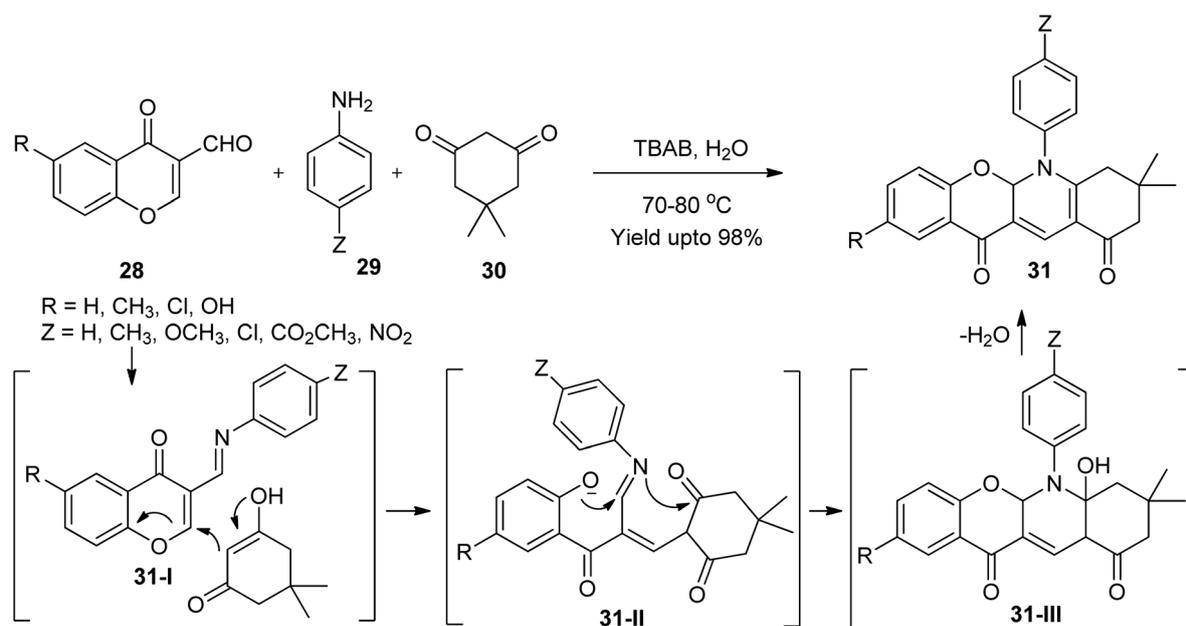
2.1.4. One-pot synthesis of 7-aryl-benzopyrano[4,3-*b*]benzopyran-6,8-diones. Using a boric acid catalyst in an SDS-micellar medium, a mild and efficient synthesis of 7-aryl-benzopyrano[4,3-*b*]benzopyran-6,8-diones (**34**) have been reported from the 4-hydroxycoumarin (**32**), aromatic aldehydes (**33**) and cyclic 1,3-diketones (**30**),⁴¹ Scheme 4. The three-component approach is significant because it addresses the issue of selectivity towards the target compounds and makes it an appropriate protocol for such a reaction to access 7-aryl-benzopyrano[4,3-*b*]benzopyran-6,8-dione constructs.

A conceptually similar protocol for the synthesis of pyrano[3,2-*c*]chromene derivatives have been reported by Abas Ali Jafar in CTAB micellar medium by reacting 4-hydroxycoumarin,

aromatic aldehydes and malononitrile.⁴² The reaction operates with the same mechanism and furnishes therapeutically important scaffolds in decent yields. In the same way another synthesis of 2-amino-4*H*-pyran derivatives was accomplished by the reaction of aldehydes, malononitrile, and cyanoketones in an aqueous CTAB micellar medium.⁴³ Furthermore, a one-pot synthesis of fluorescent coumarin-4*H*-pyran conjugates has been also established from β -ketoesters, malononitrile and aldehydes in cetyltrimethylammonium chloride (CTAC) aqueous micellar medium.⁴⁴ The study highlights the simplicity and effectiveness of this catalytic system and paving way for medicinal chemistry explorations to these coumarin derivatives.

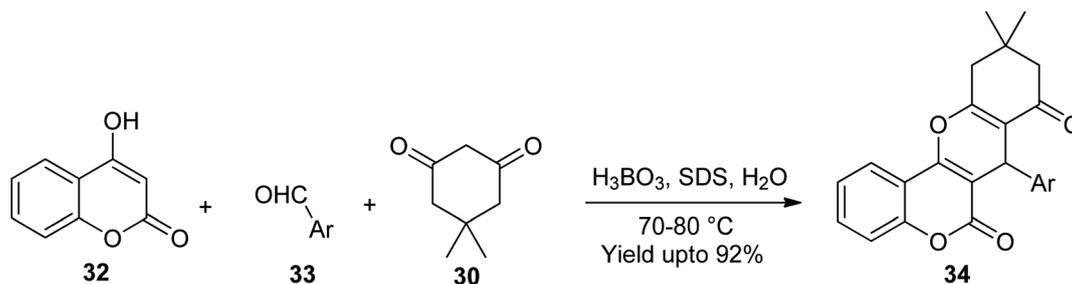
2.1.5. Synthesis of 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles. A four-component strategy for synthesizing 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles (**36**) in aqueous CTAB micellar medium using thiamine hydrochloride as a promoter is reported,⁴⁵ Scheme 5. Vitamin A-mediated amination of 3-cyanoacetyl indole (**35**) with ammonium acetate to the intermediate (**35-I**) and the resulting intermediate from it (**35-II**) reacts with the Knoevenagel condensation product, **35-III** (obtained from the aldehyde **33** and malanitrile) and its subsequent cyclization and aromatization (through intermediates **35-IV** and **35-V**) led to the formation of 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles. The resulting compounds are of significant interest in medicinal chemistry programs.

A conceptually similar four-component reaction regime has been developed by the reaction of acetophenone, benzaldehyde, arylthiol and malanitrile in Triton-X-100. Condensation of acetophenone with benzaldehyde leading a chalcone which undergoes subsequent reaction with malononitrile and



Scheme 3 A three component synthesis of chromeno[2,3-*b*]quinolinediones in aqueous TBAB micellar medium.





Scheme 4 A three component synthesis of 7-aryl-benzopyrano[4,3-b]benzopyran-6,8-diones in SDS-micellar medium.

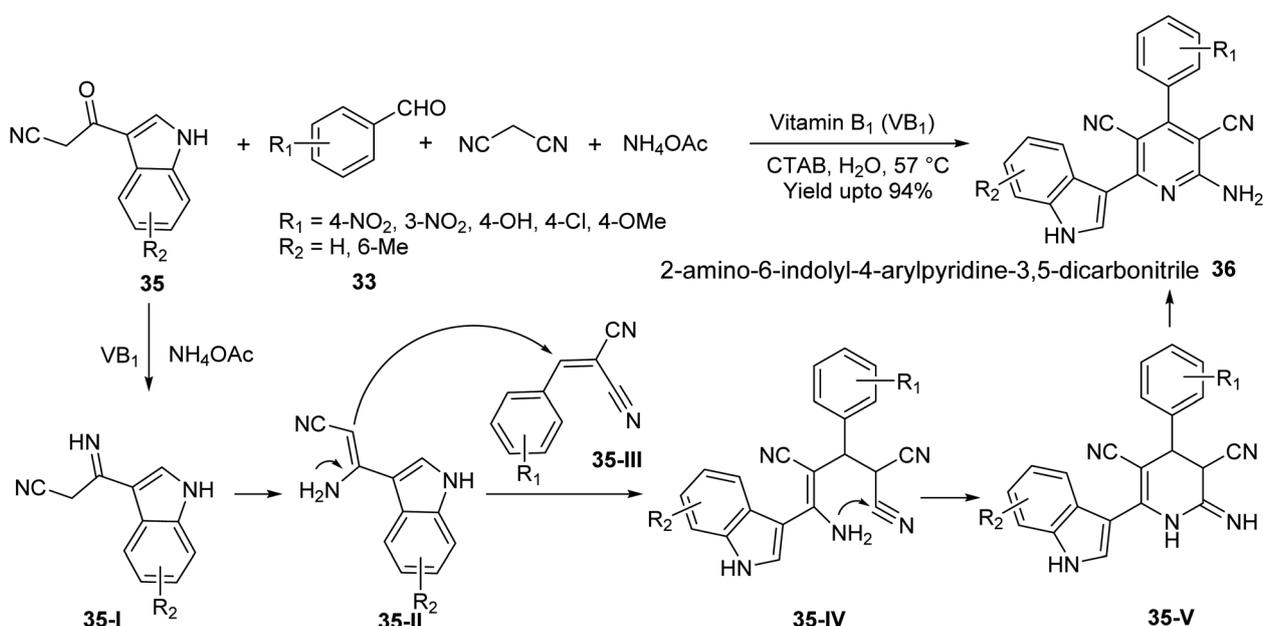
arythiol resulting in the formation of 8-substituted pyrido[2,3-*d*]pyrimidine-6-carbonitriles in excellent yields.⁴⁶

2.1.6. Synthesis of N- and O-based heterocycles and spiro-cycles. A first example of the gold-catalyzed cyclization of diols (37) to heterocycles (38) and triols to spirocycles has been reported in a designer micellar medium of TPGS-750 under ambient reaction conditions,⁴⁷ Scheme 6. This dehydrative cyclization occurs within the hydrophobic region of the micelles and thereby easily aids the dehydration. Appropriately substituted alkynes having three hydroxyl groups lead to the formation of interesting spirocycle-constructs. The findings represent the potential of micellar effects in facilitating gold-catalyzed transformations for the first time and open new avenues for sustainable synthetic methodologies for furan/pyrroles for the future.

2.1.7. Synthesis [1,2,3]-triazolyl-thiazolidinones. An interesting approach for the [1,2,3]-triazolyl-thiazolidinones using acetic acid as an organocatalyst in CTAB micellar medium has been reported,⁴⁸ Scheme 7. This method enhances the reaction efficiency by improving substrate solubility and reaction rates through the hydrophobic effects of micelles. The formation of

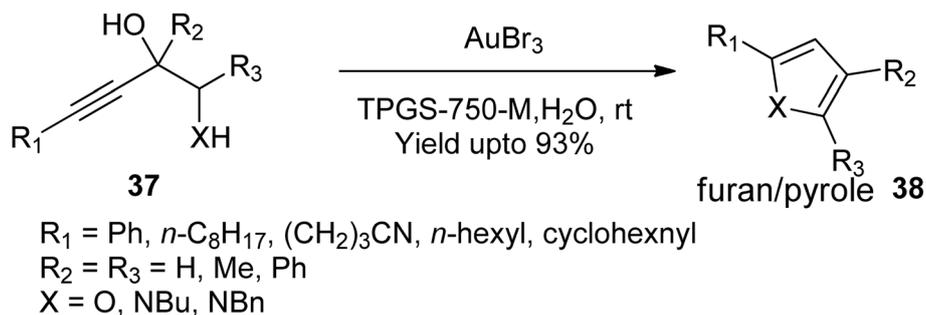
a Schiff base intermediate (**40-I**) between the aldehyde **33** and the triazole **39** is believed to occur within the micellar core wherein it reacts with mercaptoacetic acid (**40**) and leads to the desired product **41**. Surprisingly, the authors did not report any selectivity in case of these compounds formed as potential diastereomers. This Group also reported a simple strategy for the synthesis of biologically relevant compounds, 3,5-diphenyl-4,5-dihydro-1-*H*-pyrazole-*L*-carbothioamide from chalcones and thiosemicarbazide in aqueous CTAB micellar medium.⁴⁹ Notably, this methodology was also extended successfully to guanidine hydrochloride and hydrazine hydrate in place of thiosemicarbazide, resulting in a novel scaffolds of 3,5-diphenyl-4,5-dihydro-1-*H*-pyrazole and 4,6-diphenylpyrimidin-2-amine constructs. Furthermore, in another strategy, the authors reported a micelle-guided synthesis of highly functionalized 2,4-disubstituted hydrazine-thiazoles in glycerol CTAB micellar solution.⁵⁰ Broad substrate scope, fast reaction times, sustainable protocol and the use of organocatalysts are some of the highlights of these strategies.

Mahendra Nath established an interesting method for the synthesizing of spiro-indoline-3,2-thiazolidinones by reacting



Scheme 5 A four component synthesis of 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles in aqueous CTAB micellar medium.





Scheme 6 Ag-catalyzed synthesis of furans/pyroles in aqueous TPGS-750 micellar medium.

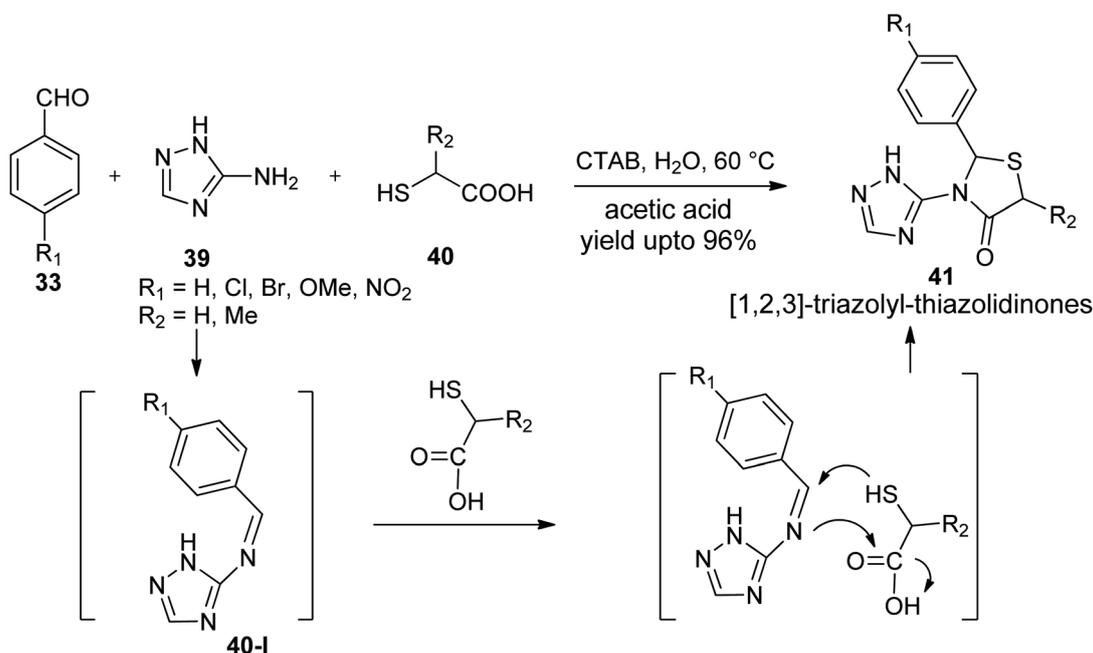
the primary amines with isatins and thioglycolic acid in micellar medium. These pharmacologically important scaffolds were synthesized through a similar set of sequential reactions in the presence of *p*-dodecylbenzene sulfonic acid (DBSA) as an efficient Bronsted acid surfactant combined catalyst in water.⁵¹

2.1.8. Synthesis of dihydro[2,3-*c*]pyranopyrazoles. Cocamidopropyl betaine (CAPB), a biodegradable and zwitterionic surfactant forming worm-like micelles in water has been employed in a four-component reaction to furnish the dihydropyrano[2,3-*c*]pyrazoles efficiently,⁵² Scheme 8. The reaction operates within the hydrophobic core of the micellar assembly leading the smooth formation of products **43** in almost quantitative yields. Condensation of hydrazine with ethylacetoacetate (**42**) generates a pyrazolone intermediate (**42-I**) which undergoes tautomerization and reaction with the Knoevenagel product (**42-II**) (formed between aldehyde and malanonitrile) to form an intermediate (**42-III**) that undergoes intramolecular cyclization to pyranopyrazole scaffold through **42-IV**. Biologically, these scaffolds are crucial in medicinal chemistry campaigns and

some of these constructs act as potent inhibitors of human chk1 kinase.⁵³

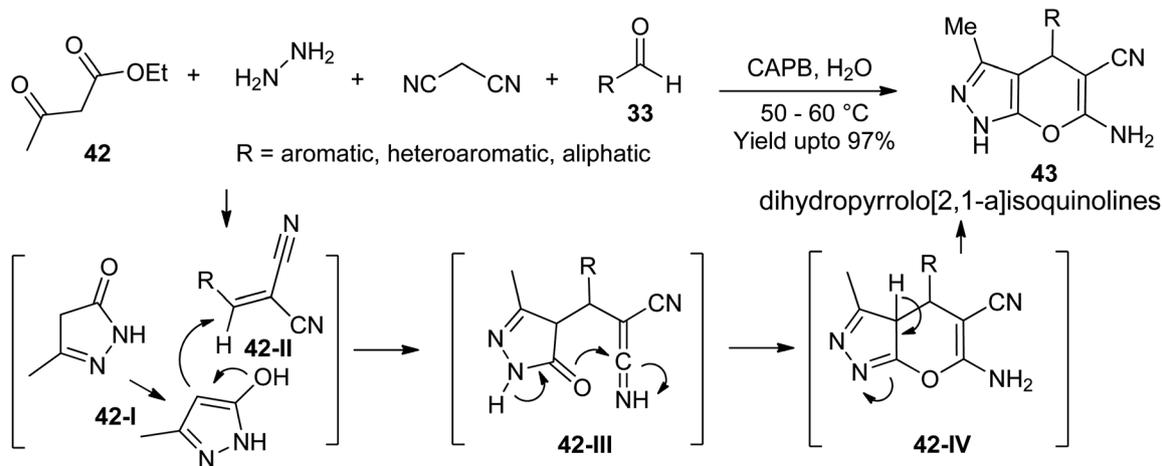
2.1.9. Synthesis of dihydropyrrolo[2,1-*a*]isoquinolines and dihydropyrrolo[1,2-*a*]quinolines via [3 + 2] cycloaddition reaction. A wide range of dihydropyrrolo[1,2-*a*]quinolones (**46**) and dihydropyrrolo[2,1-*a*]isoquinolines scaffolds were synthesized through a three-component reaction in CTAB micellar medium,⁵⁴ Scheme 9. This reaction operates in a micellar core and occurs through the formation of quaternary ammonium salt (**45-I**) between the quinolone (**44**) and phnacyl bromides (**24**). Deprotonation of intermediate **45-I** with DBU generates a nitrogen-ylide (**45-II**) which undergoes [3 + 2] cycloaddition reaction with the diethyl acetylenedicarboxylate to yield the desired compounds **46** in decent yields (Scheme 9).

2.1.10. Synthesis of hexahydrochromeno[2,3-*b*]quinoline-diones. An efficient and one-pot synthesis of 11-(chromen-3-yl)-8,8-dimethyl-8,9-dihydro-6*H*-chromeno[2,3-*b*]quinoline-10,12(7*H*,11*H*)-dione (**48**) has been accomplished by a three-component reaction involving the chromone-3-carbaldehyde



Scheme 7 Synthesis of [1,2,3]-triazolyl-thiazolidinones in aqueous CTAB micellar medium.





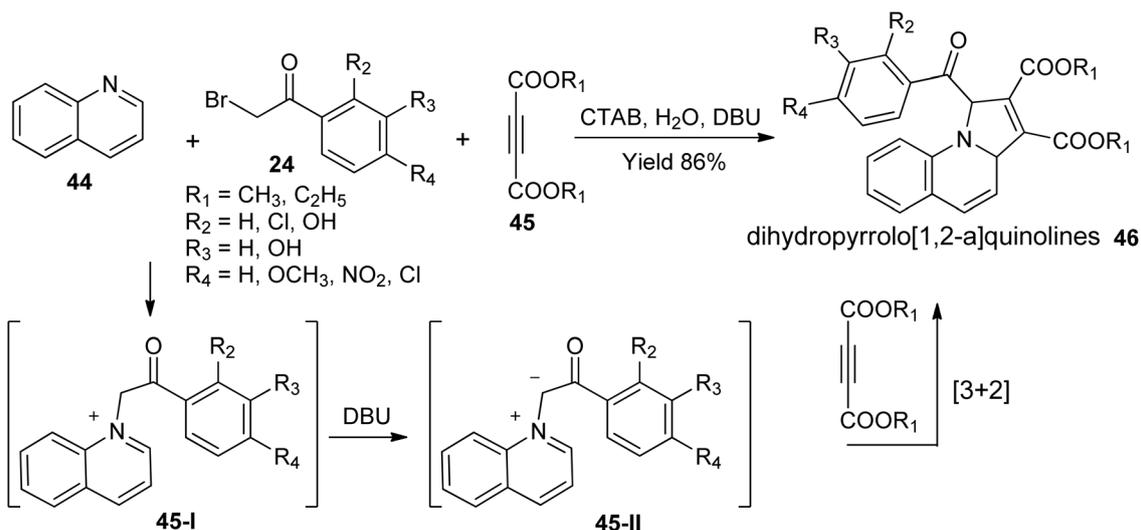
Scheme 8 Synthesis of dihydropyrrolo[2,3-c]pyrazoles in aqueous CAPB micellar medium.

(28), 2-aminochromone (47) and 1,3-cycloakadione (30) in aqueous SDS-micellar medium,⁵⁵ Scheme 10. This reaction occurs in an anionic micellar solution and operates through a mechanism similar to the above mentioned reactions (*cf.* Scheme 3).

2.1.11. Selective strain-promoted azide-alkyne cycloaddition. An interesting strain-promoted azide-alkyne cycloaddition (SPAAC) reaction has been reported through micellar catalysis in an aqueous medium,⁵⁶ Scheme 11. These bioorthogonal site selective reactions have gained considerable traction in recent years as they enable site-specific tagging of biomolecules. In the current protocol, the reactivity of azides (50) with alkynes was enhanced many folds in a CTAB micellar solution. Furthermore, the reaction selectivity of hydrophobic azide, benzyl azide (51) has been enhanced 51-fold than the hydrophilic azides PEG3 (52). These findings are expected to have huge implications in bioorthogonal chemistry and pharmaceutical chemistry for future drug discovery programs (Scheme 11).

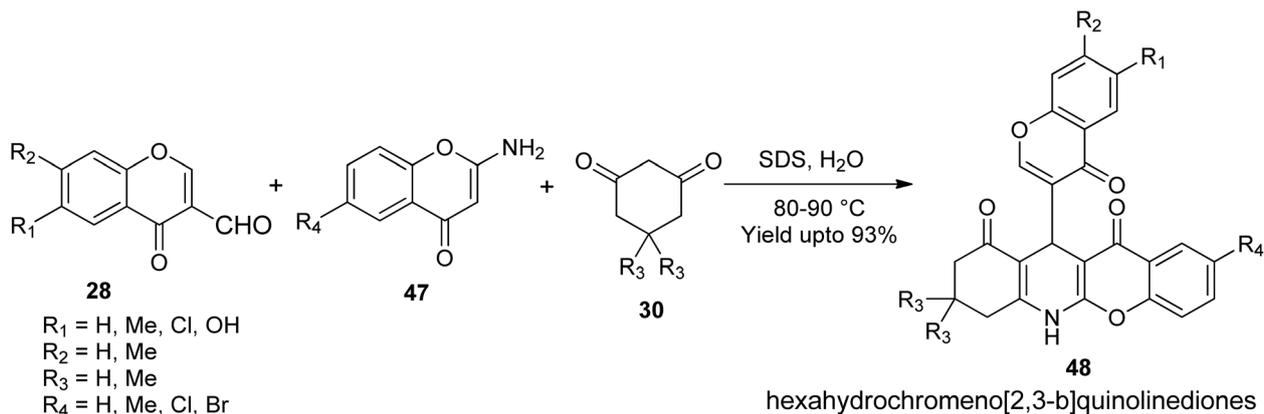
2.1.12. Synthesis 5-phenylbenzopyrimido [4,5-*b*]quinolones. An interesting nano ZnO-mediated synthesis of 5-phenylbenzopyrimido[4,5-*b*]quinolones (55) has been accomplished from the 2-hydroxynaphthalene 1,4-dione (53) aldehydes (33) and 6-aminouracil (54) in aqueous CTAB-micellar medium,⁵⁷ Scheme 12a. This protocol is unique in the sense that it involves the nanoparticle-guided synthesis of desired products in micellar nanoreactors through a sustainable fashion. The reaction operates on the ZnO-surface involving the condensation of 2-hydroxynaphthalene1,4-dione 53 with the aldehyde to intermediate 55-I followed by its stitching with the 6-aminouracil. Overall, these findings highlight the compatibility of micellar nonreactors with nanoparticle catalysts and furnish the desired products expeditiously.

A conceptually similar protocol was developed by Ali Khalafi Nezhad *et al.* using polyethylene glycol-bonded 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU-PEG), a new surfactant-combined base



Scheme 9 A three component synthesis of dihydropyrrolo[1,2-a]quinolines in aqueous CTAB micellar medium.





Scheme 10 A three component synthesis of 11-(chromen-3-yl)-8,8-dimethyl-8,9-dihydro-6*H*-chromeno[2,3-*b*]quinoline-10,12(7*H*,11*H*)-dione SDS micellar medium.

catalyst for the multicomponent synthesis of 8-substituted pyrido[2,3-*d*]pyrimidine-6-carbonitriles (**58**),⁴⁶ Scheme 12b. This reaction in water involving multicomponents like aldehydes, malononitrile, barbutiric acid (**56**) and nucleosides (**57**) in PEG-DBU surfactant furnishing 8-substituted pyrido[2,3-*d*]pyrimidine-6-carbonitrile (**58**) scaffolds in excellent yields.

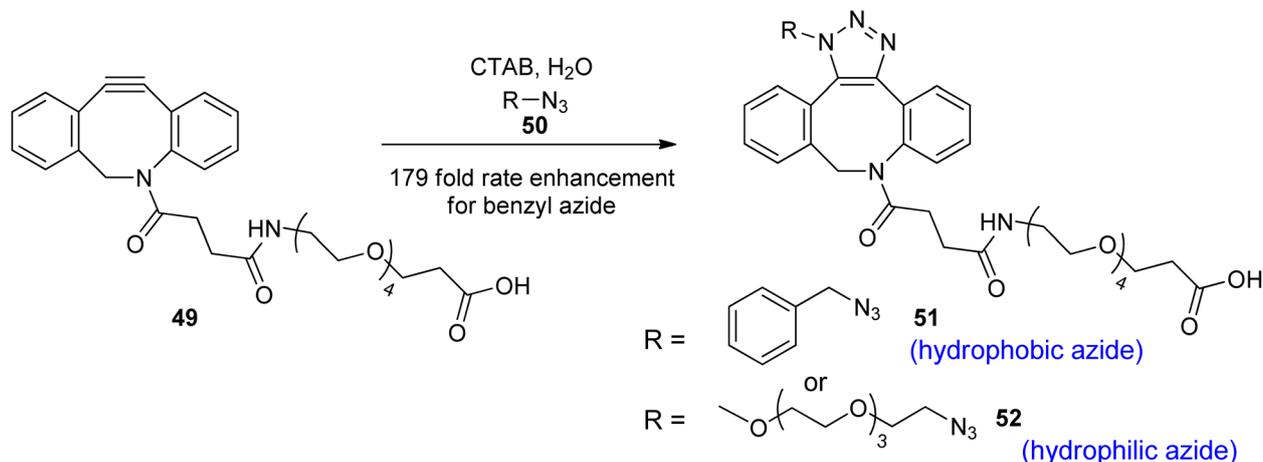
2.1.13. Synthesis of 4-phenylsulfonamido-6-aryl-2-phenylpyrimidine-5-carbonitriles. An efficient and straightforward method for synthesizing 4-phenylsulfonamido-6-aryl-2-phenylpyrimidine-5-carbonitriles (**60**) has been reported in an aqueous micellar medium,⁵⁸ Scheme 13. This method involves the reaction between aldehydes (**33**), malononitrile and benzamide hydrochloride (**21**) to furnish the phenylpyrimidine construct and its subsequent reaction with the benzenesulphonyl chloride (**59**) generates the desired product in quantitative yields.

2.1.14. Synthesis of quinazolinones. A convenient method for synthesizing quinazolinones (**63**) using copper as a catalyst in an aqueous medium with the aid of designer surfactant TPGS-750-M has been reported,⁵⁹ Scheme 14. In this method, the 2-halobenzoic acids (**61**) derivatives couples with the

amidines and guanidines (**62**) furnishing the desired quinazolinones in excellent yields. Mechanistically, the reaction goes through copper intermediates **61-I–61-II** followed by the cyclization of the intermediate **61-III**. As expected, the E-factor of this protocol is significantly higher than the conventional methods and these scaffolds are integral part of many natural products and bioactive agents with varied biological activities.⁶⁰

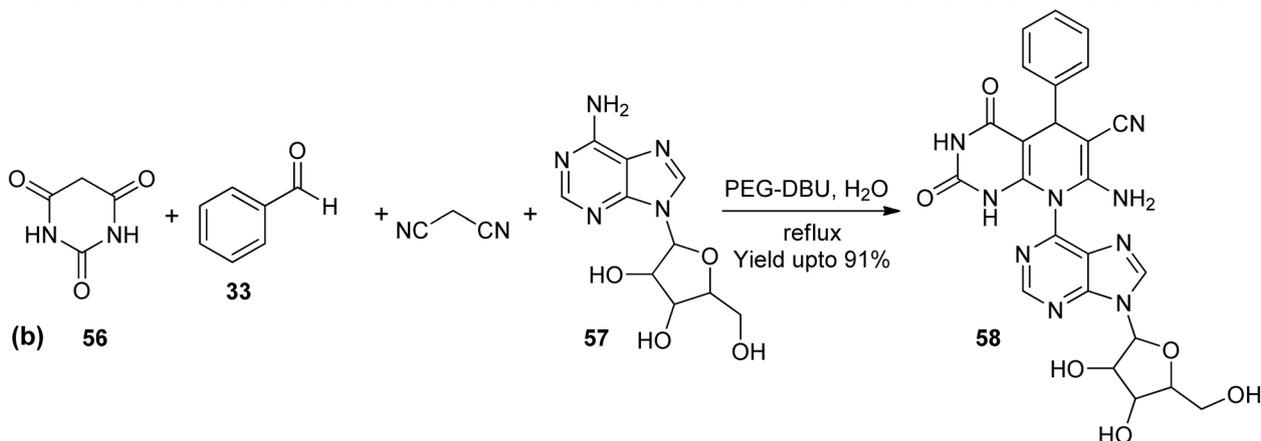
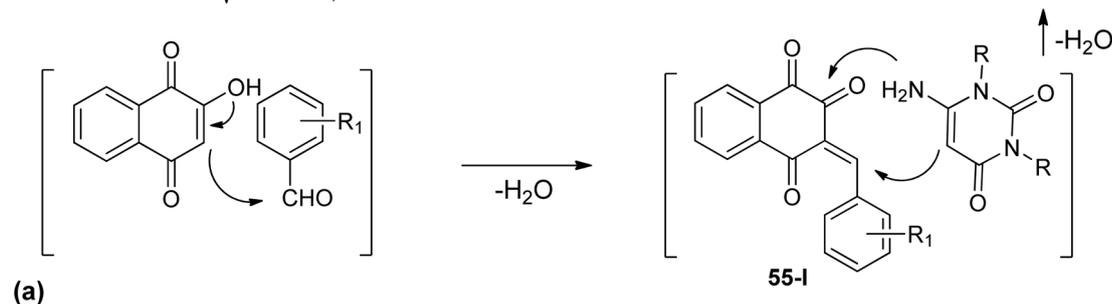
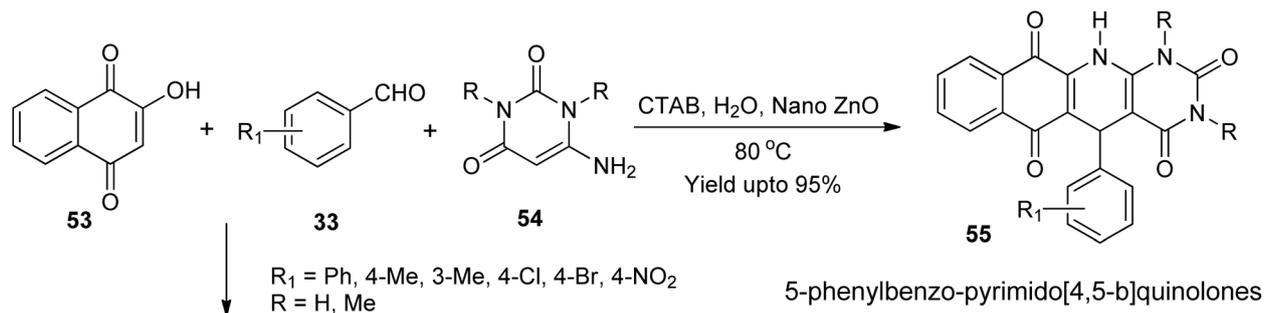
2.1.15. Synthesis of spiro-fused piperidine derivatives. Employing an iron(III)trifluoroacetate in aqueous SDS micellar solution, cyclo-condensation reaction of dimedone (**30**), amines and formaldehyde furnishing the 3,5-disubstituted piperidines derivatives (**64**) in excellent yields,⁶¹ Scheme 15. In this reaction six molecules of reactants condense to create six new covalent-bonds in a single pot during the double amino methylation involving a cascade of methenylation, Michael addition and double Mannich reaction through intermediates **30-I** to **30-III**. Most of these spiro-scaffolds exhibited decent antibacterial efficacy as compared to the standards.

2.1.16. Synthesis of (*E*)-6-phenyl-7-styryl-5,6-dihydrodibenzo[*b,h*][1,6] naphthyridines. An interesting synthesis of (*E*)-6-phenyl-7-styryl-5,6-dihydro-dibenzo[*b,h*][1,6]



Scheme 11 A selective strain-promoted azide-alkyne cycloaddition in aqueous micellar medium.

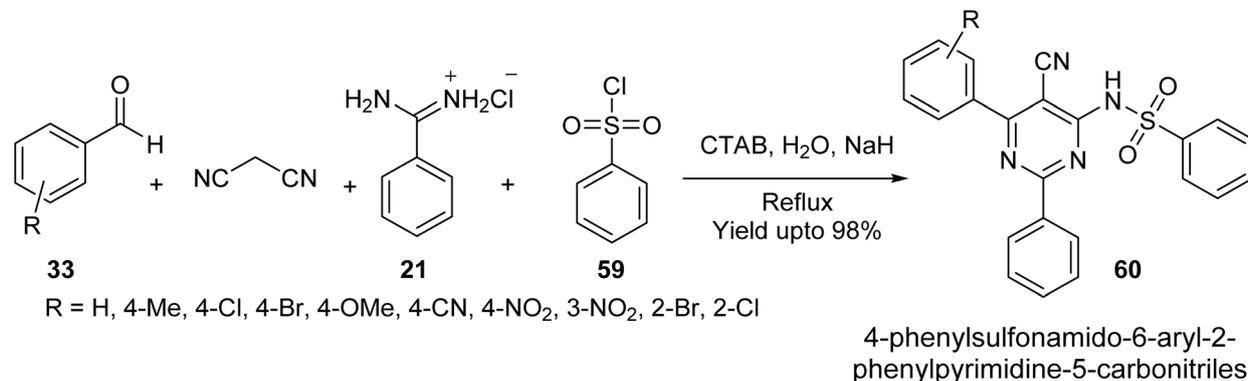




Scheme 12 (a) A nano-ZnO catalyzed synthesis of 5-phenylbenzopyrimido[4,5-b]quinolones in aqueous CTAB micellar medium; (b) a multi-component synthesis of 8-substituted pyrido[2,3-d]pyrimidine-6-carbonitriles using aqueous PEG-DBU.

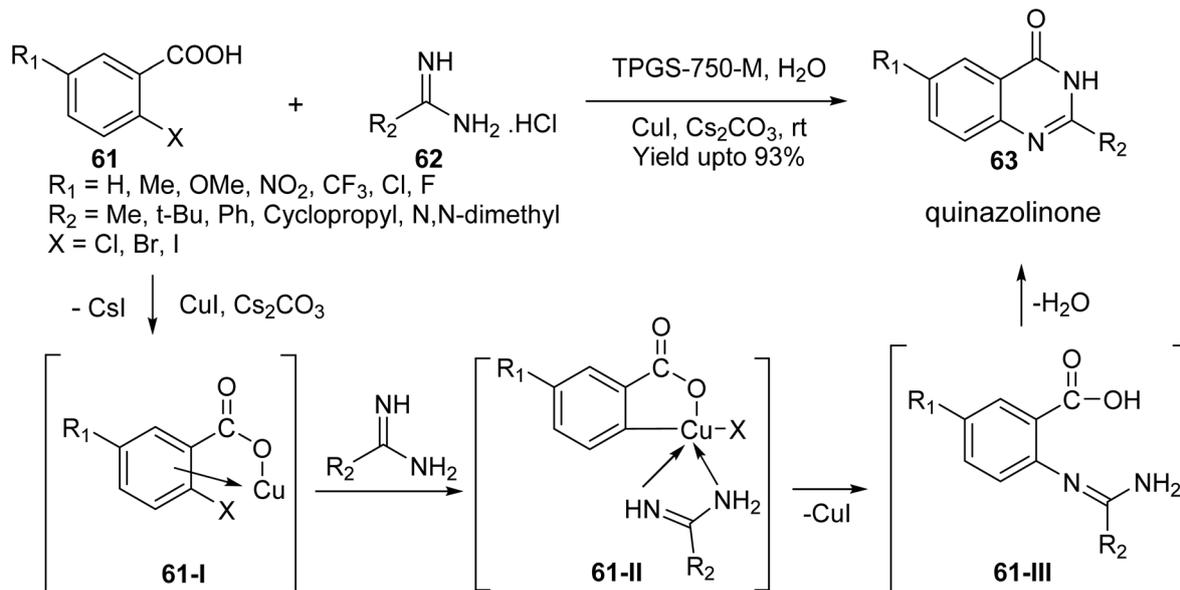
naphthyridines (**66**) have been reported from the amino chalcones (**65**) in aqueous SDS-micellar medium,⁶² Scheme 16. This reaction involves a cascade of transformations involving an

intramolecular aza-Michael addition to intermediate **65-I** and its Friedlander condensation with the chalcone in the presence of Brønsted acid furnishing the desired compounds in decent



Scheme 13 NaH-mediated synthesis of 4-phenylsulfonamido-6-aryl-2-phenylpyrimidine-5-carbonitriles in aqueous micellar medium.





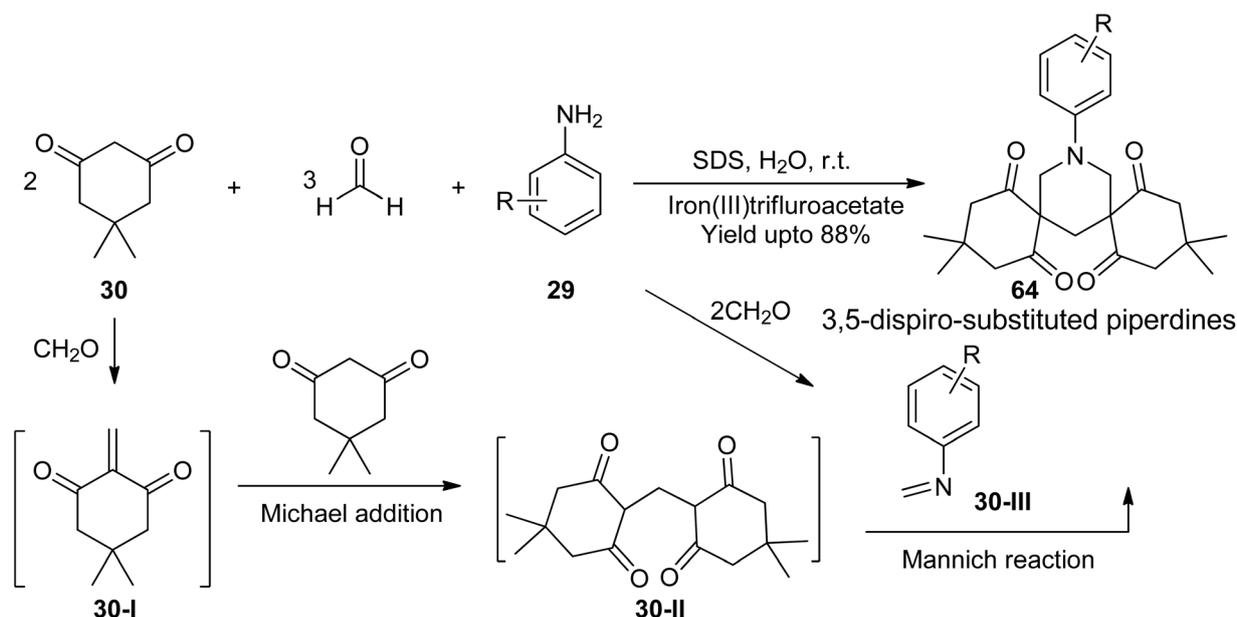
Scheme 14 Cu-catalyzed synthesis of quinazolinones in aqueous TPGS-750-M micellar medium.

yields. These compounds are expected to have great implications in medicinal chemistry campaigns.

2.1.17. Synthesis of 3-ethylcarboxylate coumarin. The use of 1-(2-pyrimidyl)piperazine (2-PP) as an organobase catalyst in a micellar medium has been explored to access 3-ethylcarboxylate and 3-acetyl coumarins (**67**) in aqueous SDS micellar medium,⁶³ Scheme 17. By leveraging the micellar environment, the study demonstrates improved catalytic performance and stability of the organobase, facilitating easier recovery and reuse in multiple reaction cycles. This approach not only enhances the efficiency of catalysis but also addresses

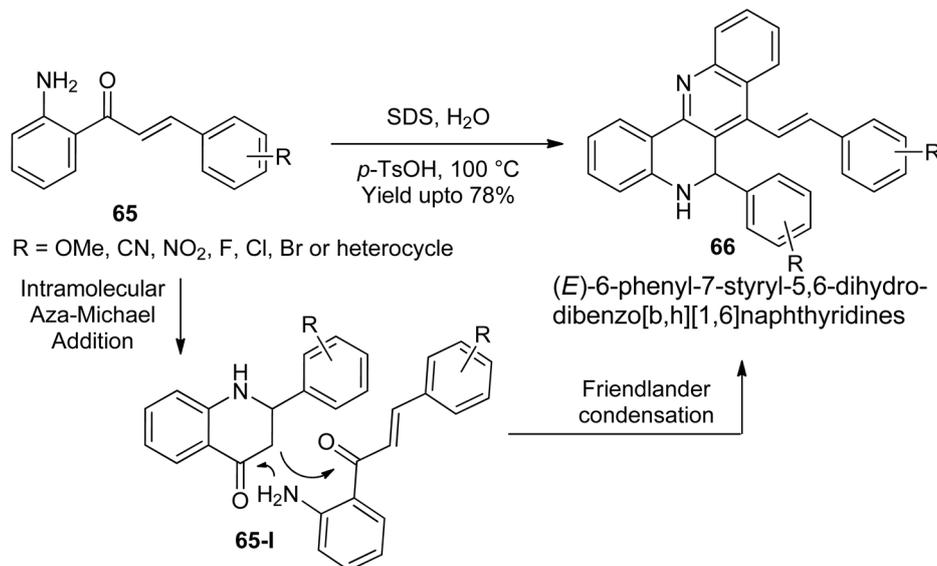
sustainability concerns by reducing waste and promoting the longevity of the catalyst, making it a valuable strategy for advancing organocatalysis in organic synthesis.

2.1.18. Synthesis of pyrroles and indoles. A divergent reactivity of α -azidochalcones (**68**) has been reported when reacted with metal β -diketonates furnishing the substituted pyrroles (**69**) and indoles (**70**) in aqueous micellar medium and organic medium respectively,⁶⁴ Scheme 18. By varying the metal and reaction conditions from aqueous to organic, the authors achieved tunable product profiles demonstrating the versatility of this reaction to access diverse heterocyclic compounds.



Scheme 15 Fe(III)-catalyzed synthesis of 5-dispirosubstituted piperidines in aqueous SDS-micellar medium.





Scheme 16 PTSA-mediated (E)-6-phenyl-7-styryl-5,6-dihydro-dibenzo[b,h][1,6]naphthyridines in aqueous SDS-micellar medium.

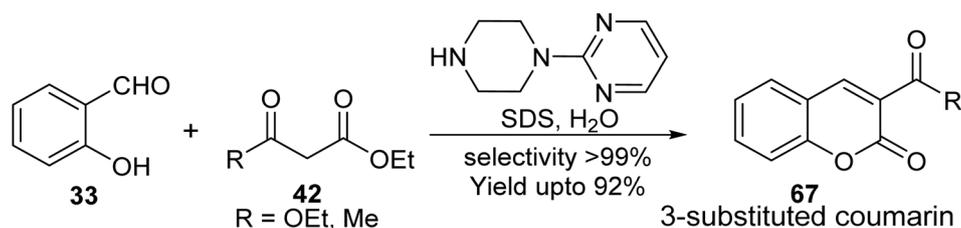
Notably, both the reaction goes through aziridine-intermediate and subsequently diverts in the latter stages to yield the desired products. These findings suggest potential applications of micellar-catalysis in developing new compounds with significant implications in medicinal chemistry and materials science.

2.1.19. Synthesis of quinolone-4-carboxylic acid. An efficient approach to the Pfizinger reaction by employing cetyltrimethylammonium hydroxide (CTAOH) surfactant catalysis has been reported to synthesize quinoline-4-carboxylic acids (73),⁶⁵ Scheme 19. The reaction operates from the isatins (71) to isatoic acid (71-I) which condenses with the ketone to intermediate 71-II-71-III and its subsequent cyclization furnishes the desired product in decent yields. It was concluded that this reaction occurs within the palisade region of the micellar assemblies and the reaction partners are mainly attracted by electrostatic and hydrophobic interactions within the micellar cavities.

2.1.20. Synthesis of spiro[dihydroquinoline-naphthofuranone] constructs. A one-pot, catalyst-free synthesis of spiro[dihydroquinoline-naphthofuranone] (76) constructs have been accomplished by reacting isatins (71) with β -naphthol (74) and 1,3-cyclodiones (75) in water,⁶⁶ Scheme 20. The reaction exploits hydrogen bonding effects to promote the formation of these complex constructs and operates through

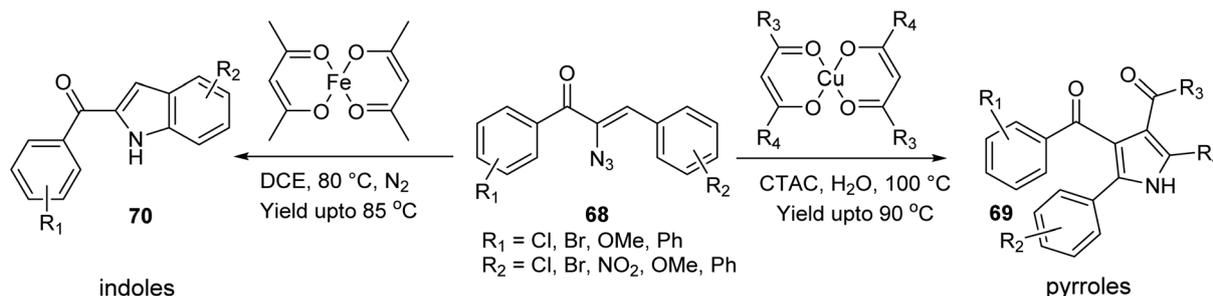
the Knoevengel-condensation reaction of isatins with 1,3-cyclodiones and the resulting intermediate (76-I) undergoes Michael addition with β -naphthol and its further structural reorganization (76-II-76-III) furnishes the desired scaffolds in decent yields. This study highlights the simplicity of the method, demonstrating its successful construction of diverse spiro-compounds without the need for additional catalysts, thereby contributing to highly sustainable synthetic methodologies in organic synthesis for building complexities.

2.1.21. Synthesis of 1,3-oxazine scaffolds. An efficient, one-pot multicomponent synthesis of pharmaceutically relevant [1,3]oxazine constructs (77) has been developed using iron-trifluoroacetate ([Fe(CF₃CO₂)₃]) as Lewis acid in an aqueous SDS-micellar solution,⁶⁷ Scheme 21. Mild reaction conditions, high yield of products, easy purifications and sustainability of the methodology are some of its salient features. The reaction operates in a micellar medium through iron(III)-catalyzed Mannich-type condensation of anilines (29) with formaldehyde and the resulting intermediate reacts with the β -naphthol (74) to form the intermediate 74-I & 74-II. The latter undergoes a second Mannich condensation with formaldehyde to form the intermediate 74-III and its cyclization yielded the desired product, 77. Notably, this reaction was also implemented on α -



Scheme 17 2-PP-mediated synthesis of 3-ethylcarboxylate- and 3-acetyl coumarin in aqueous SDS-micellar medium.





Scheme 18 A divergent synthesis of pyroles and indoles in aqueous CTAC-micellar medium and DCE respectively.

naphthol, 4-hydroxy-coumarins and 2-hydroxy-coumarins to furnish a diverse range polyaromatic[1,3]oxazine constructs.

2.1.22. Synthesis of imidazole[1,2-*a*]pyridines. An efficient and environmentally friendly method for imidazole[1,2-*a*]pyridine (**80**) through a Cu-ascorbate-catalyzed A³-coupling reaction in aqueous micellar media has been reported,⁶⁸ Scheme 22. This approach serves as a sustainable catalyst and solvent system, promoting a significant reduction in waste and is aligned with the ideas of green and sustainable chemistry. The reaction operates in water by a dynamic combination of Cu(II)/Cu(I) generated *in situ* and guided a facile 5-*exo-dig* cycloisomerization between alkynes (**79**) with imines (generated from aldehydes and amines) to furnish the desired product through the intermediacy of **78-I** to **78-III**.

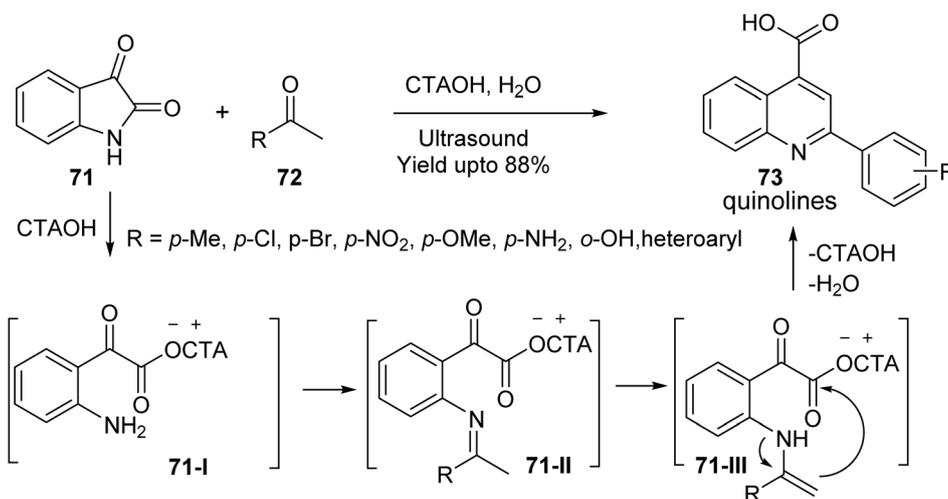
2.1.23. Synthesis of pyrrole derivatives. MGSFe, a highly paramagnetic catalyst synthesized from the gemini surfactant (GS) by reacting with ferric chloride has been reported to synthesize pyrroles in deep eutectic solvents,⁶⁹ Scheme 23. This reaction occurs through the benzoin condensation of aldehydes to benzoin (**81**) and their subsequent reaction with the 1,3-diketones/alkylacetoacetates in the presence of ammonium acetate furnishes the desired pyrroles (**82**) in decent yields.

2.1.24. Synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives. An easy and one-pot synthesis of 2,3-

dihydroquinazolin-4(1H)-ones (**84**) using anthranilamide (**83**) and benzaldehyde have been reported in aqueous reverse ZnO-nanomicelles,⁷⁰ Scheme 24. To entangle ZnO, CTAB reverse nano-micelles were initially generated in cyclohexane and subsequently zinc to furnish the reverse ZnO CTAB-nanomicelles. The reaction operates by the aniline-benzaldehyde condensation followed intramolecular cyclization with the amide within the core region of the reverse-ZnO nanomicelle to furnish the desired products quantitatively.

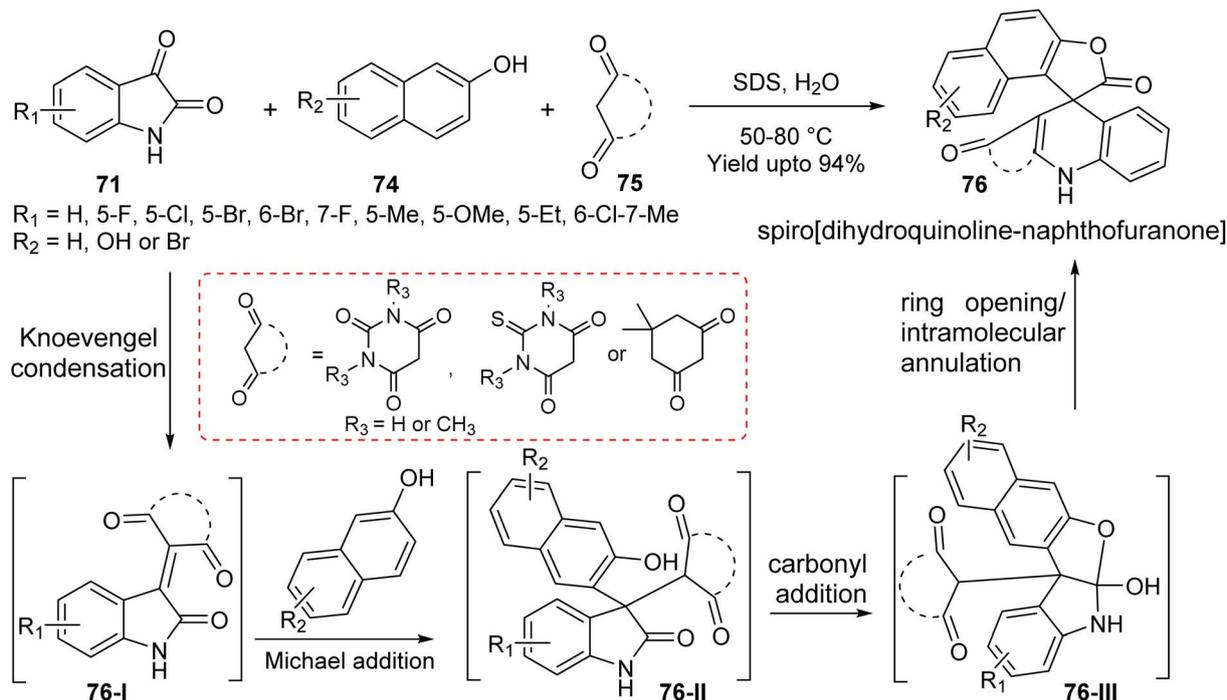
Later on, a new method for quinazolinones and spiro-quinazolinones has been accomplished through a multicomponent reaction of isatoic anhydride, amine and aldehydes/istanins.⁷¹ This reaction is catalyzed by L-proline, occurs in Triton-X-100 micellar medium and bears vast structural diversity.

2.1.25. Synthesis of indolylbenzothiazole. A nanomicellar catalytic method for the synthesis of 2-(indol-3-yl)benzothiazoles (**87**) in water in designer surfactants TPGS 750-M have been accomplished,⁷² Scheme 25(a). This reaction occurs between the 2-aminothiophenol (**85**) and the indole carbaldehyde (**86**) operates through the dehydrative cyclization to thiazoline intermediate (**85-II**) and its *in situ* oxidation delivers the desired compounds in decent yields. Furthermore the authors have utilized these compounds for further



Scheme 19 Synthesis of quinolines in aqueous CTOH-micellar medium.





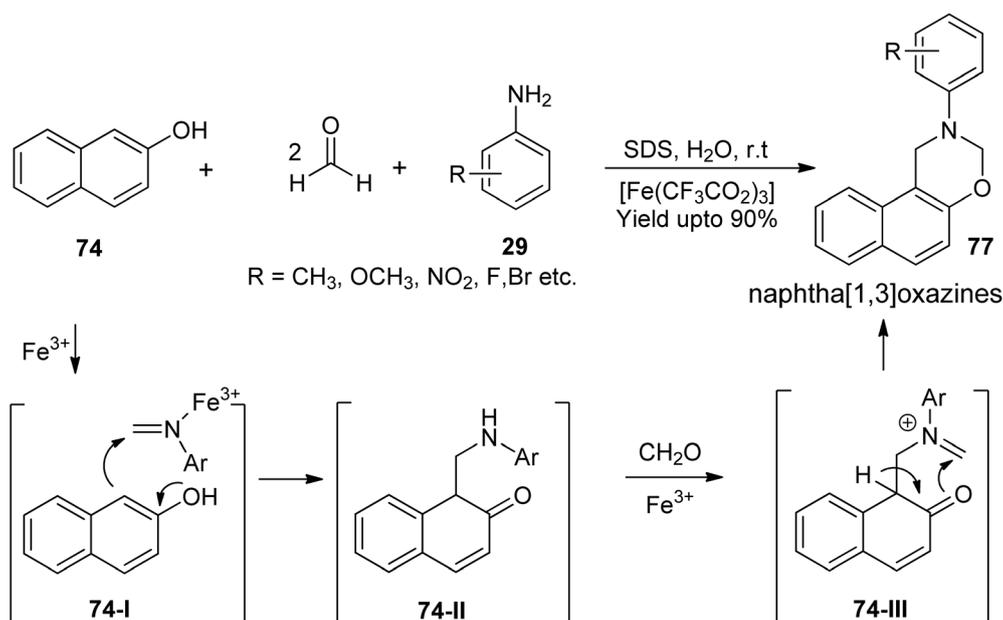
Scheme 20 Synthesis of spiro[dihydroquinoline-naphthofuranone] in aqueous SDS micellar medium.

functionalization to construct tris-heterocyclic scaffolds *via* benzothiazole directed Mn(II)-catalyzed C_2 -H amination with pyridines as amine partners.

A conceptually related synthesis of 4*H*-pyrimido [2,1-*b*]benzothiazoles (**89**) have been accomplished separately from through a multicomponent cyclocondensation reaction of β -ketoester (**42**), aromatic aldehydes (**33**) and 2-amino-benzothiazole (**88**) reaction partners,⁷³ Scheme 25(b). This

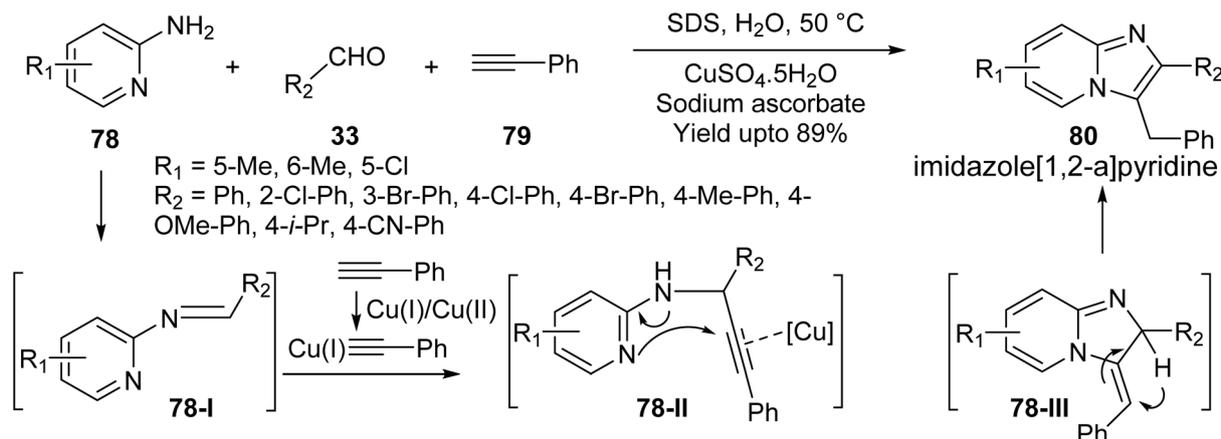
reaction has been accomplished in CPB micellar solution using DBU as an organic base.

2.1.26. Synthesis of chromenoquinoline derivatives. A new series of amphiphiles, *N*-acyl-*N*-(pyridin-2-ylmethyl)glycines (PyNAG) with variable chain lengths from glycine have been synthesized and utilized in organic transformations. The ability of the PyNAG micelles to execute important organic transformations in water was demonstrated through synthesizing



Scheme 21 Synthesis of naphtha[1,3]oxazines in aqueous SDS micellar medium.



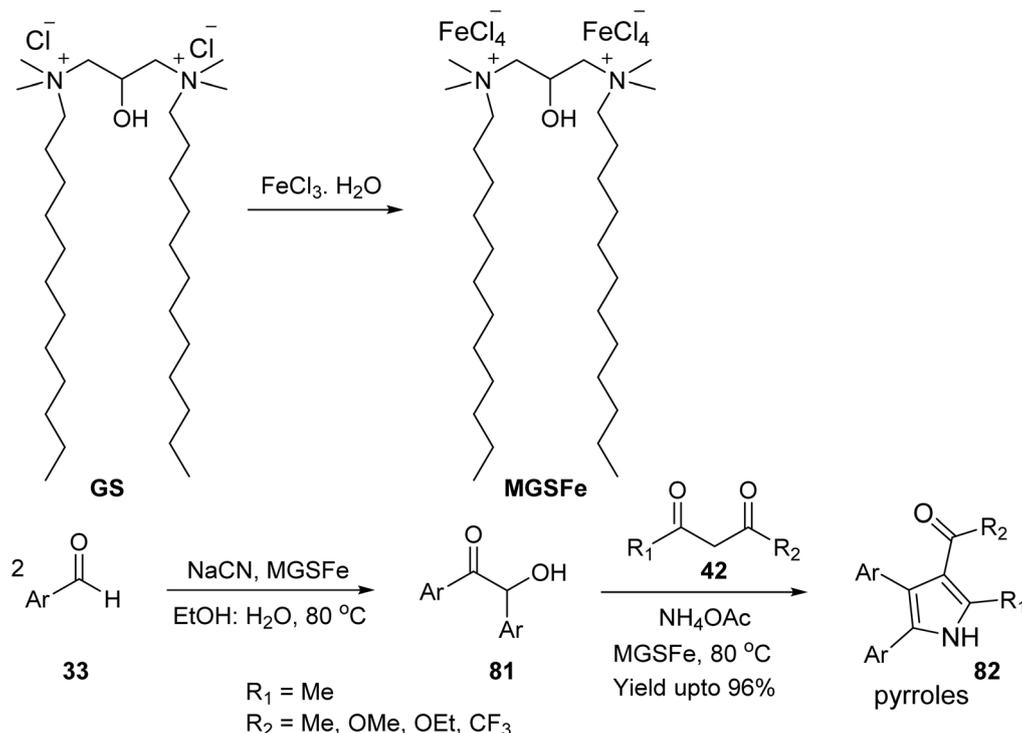


Scheme 22 Cu-catalyzed synthesis of imidazole[1,2-a]pyridine in aqueous SDS micellar medium.

chromenoquinoline (**91**) via the Povarov reaction,⁷⁴ between the alkyne **90** and aniline **29**, Scheme 26. This reaction produced a good results in *N*-stearoyl-*N*-(pyridin-2-ylmethyl)glycine (PyN18G) micelles and it has been observed that the micellar interior significantly affected the reactivity of the substrate. The authors suggested that these observations should be taken into consideration while creating new media for metal-catalyzed reactions for sustainable organic synthesis.

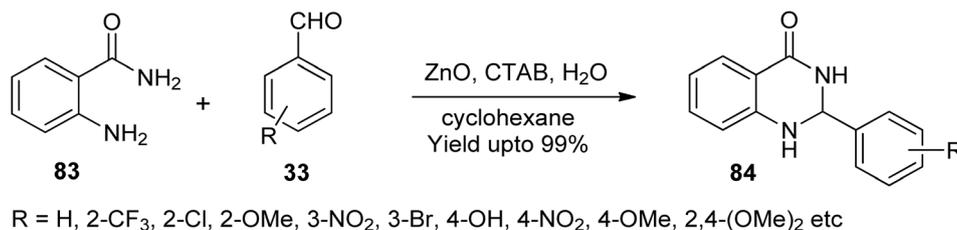
2.1.27. Synthesis of quinoxaline, 1,4-benzoxazine and 1,4-benzothiazine constructs. In heterocyclic chemistry, our group has developed an environmentally friendly and multicomponent protocol for accessing a range of heterocyclic compounds,

quinoxalines (**97**), 1,4-benzoxazines (**94**) and 1,4-benzothiazines (**95**) from the styrenes (**92**) in aqueous micellar assemblies using a less common CPB surfactant,⁷⁵ Scheme 27. This reaction operates in a micellar environment through a number of sequential steps involving regioselective bromination of styrene and NBS-mediated oxidation of the resulting intermediate (**92-I** and **92-II**) to phenacyl bromide. Condensation of the latter with 1,2-diamino benzene (**96**), 2-aminophenol and 2-aminothiophenol (**93**) furnished the quinoxaline, 1,4-benzoxazine and 1,4-benzothiazine scaffolds in decent yields. NMR studies of the solubilizates confirmed that the reaction operates within the stern region of the micellar assemblies. Based on the DFT



Scheme 23 MGSFe-catalyzed synthesis of pyrroles in micelles.





Scheme 24 Reverse ZnO-nanomicelle catalyzed synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones micellar medium.

calculations and other theoretical studies confirmed that the CPB-micelles exhibited a vander Walls type of affinity towards the solubilizates through a cation- π interaction leading to the products in decent yields.

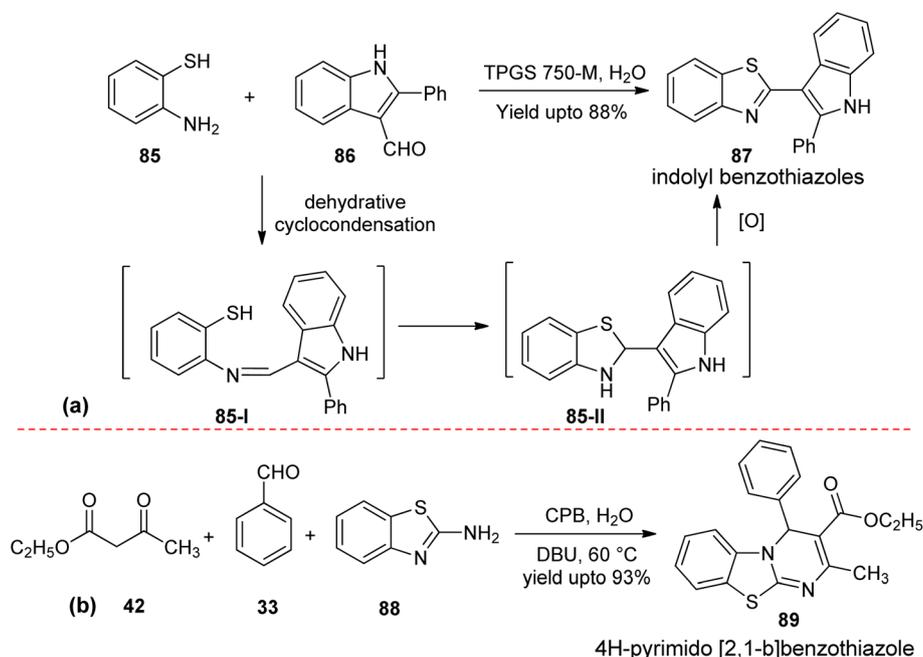
2.2. Micellar-catalysis in the synthesis of natural products and natural products scaffolds

After a considerable success in heterocyclic chemistry, micellar catalysis is also gaining interest in the synthesis of natural products/scaffolds through cascade reactions. Though this field is in infancy, the following examples will motivate the organic chemists to explore it in future.

2.2.1. Synthesis of cannabinoids. In this article, an interesting synthesis of cannabinoids have been accomplished by reacting the olivetol (**98**) with citral (**99**) using the biomimetic approach in water,⁷⁶ Scheme 28. Notable the reactivity and regioselectivity of the reactions are different using “on water” and “in water” chemistry. In water, the reaction followed the C2-regioselectivity and furnished the cannabichromene (CBC, **101**) analogue as a major compound while as in the presence of SDS surfactant, it resulted into the formation of

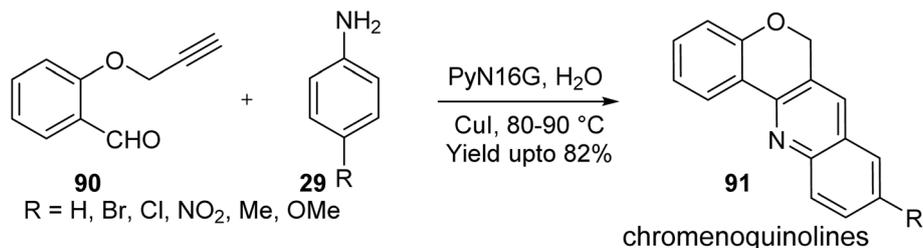
tetrahydrocannabinol (THC, **100**) derivative following the C4-regioselectivity. The plausible mechanism of formation of different products during “on water” and “in water” reaction conditions involve a cascade of sequential reactions involving various intermediates captured in the Scheme 28. PGSE diffusion and NOESY NMR studies were carried to establish the interactions of olivetol with citral with the SDS-micellar solution that drives the regioselectivity of the THC products in the presence of micellar medium.

2.2.2. Photochemical induced selectivity of estrone derivatives using photo-Fries rearrangement. A photochemical reaction of 3-acetylestro-3-one (**102**) and 3-benzoylestro-3-one (**105**) derivatives have been studied in organic and aqueous micellar media for the selectivity purpose. The outcome of this reaction in cyclohexane was completely non-selective and furnished as many as five potential products. However, shifting from the organic to micellar medium (cationic, neutral or anionic) resulted selectivity in the formation of various products. Notably, the best results were obtained in the Brij-35 micellar medium in which the 2-acetyl (**103**) and 4-acetylestro-3-one (**104**) were obtained in 59% and 33% respectively while as 2-benzoyl



Scheme 25 (a) Synthesis of 2-(indol-3-yl)benzothiazoles and (b) 4*H*-pyrimido [2,1-*b*]benzothiazoles in micellar medium.

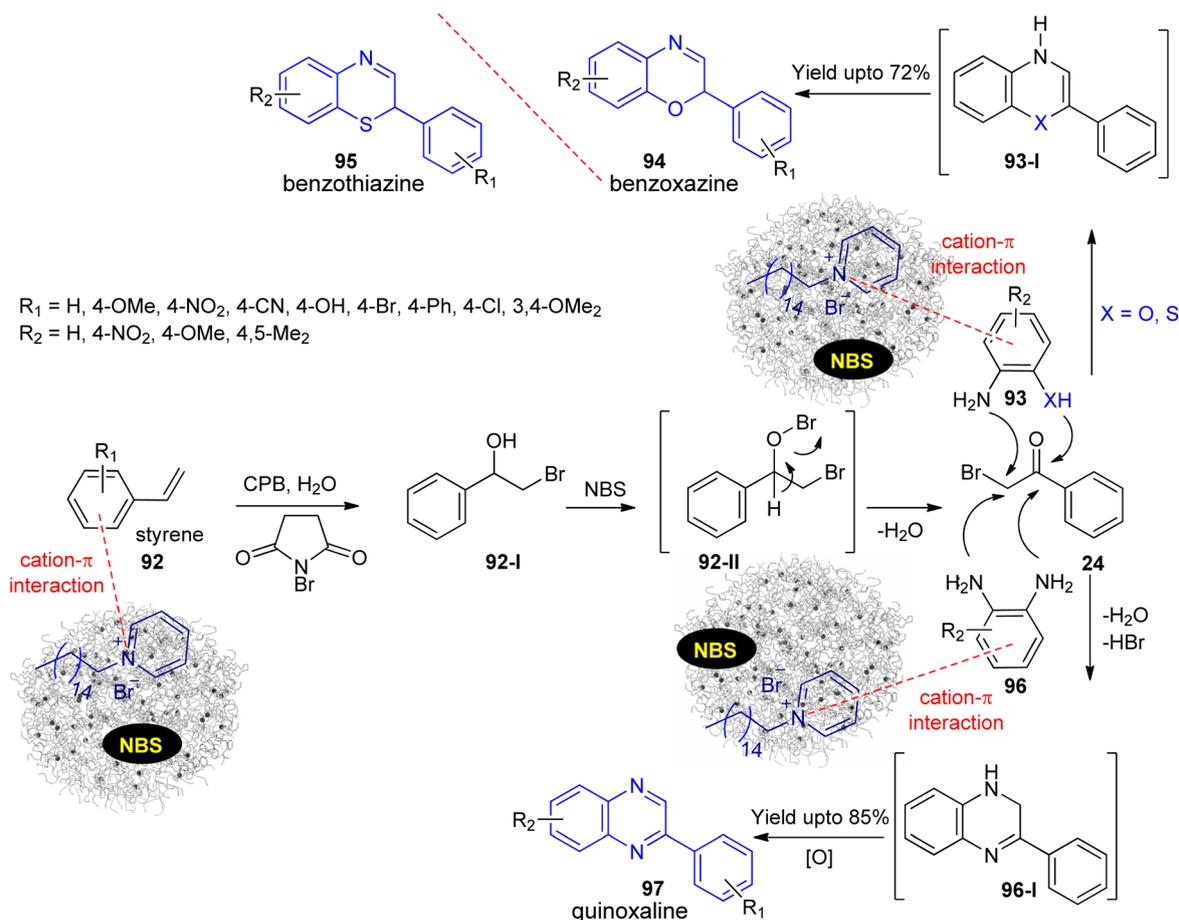


Scheme 26 Synthesis of chromenoquinoline *via* the Povarov reaction C in aqueous PyNAG-micellar medium.

(106) and 4-benzoylestrore (107) were obtained in 70% and 11% yield respectively,⁷⁷ Scheme 29. Furthermore, during these transformations, the position of the steroidal constructs within the hydrophobic core of the micelle and the binding constant has been determined using UV-visible and 2D-NMR (NOESY) spectroscopies.

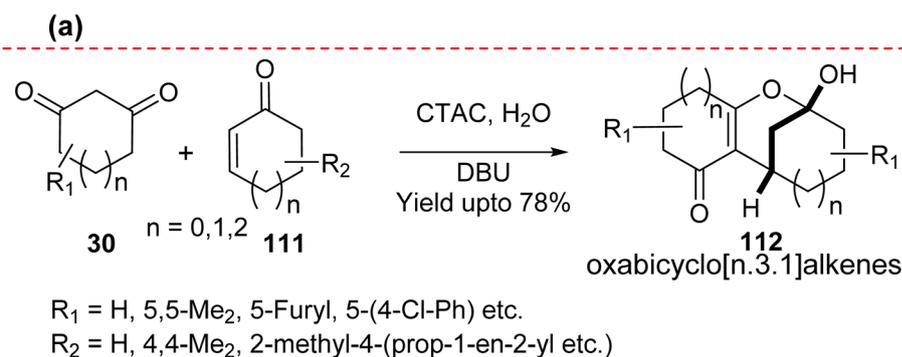
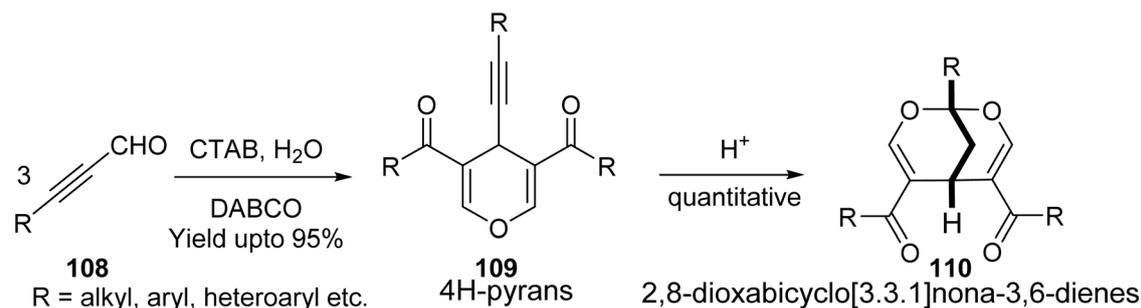
2.2.3. Synthesis of bridged bicyclic constructs, 2,8-dioxabicyclo[3.3.1]nona-3,6-dienes and oxabicyclo[*n*.3.1]alkene frameworks. In pursuit for the sustainable synthesis of natural products and natural product constructs, our research group has been engaged in developing novel strategies towards bioactive constructs inspired from nature. In this connection,

we have developed an interesting strategy for the construction of a diverse array of 2,8-dioxabicyclo[3.3.1]nona-3,6-diene (110) constructs present in natural products. Initially, a micelle guided reaction was developed to trimerize terminal ynals (108) into 4*H*-pyran (109) constructs in aqueous CTAB micellar medium in the presence of CTAB. This reaction operates in micellar nano-reactors involving a cascade of steps to deliver 4*H*-pyrans. Exposure of latter with the triflic acid re-organized them into highly functionalized 2,8-dioxabicyclo[3.3.1]nona-3,6-diene scaffold (110) in quantitative yields,⁷⁸ Scheme 30(a). Taking cue from these experiences we next sought access another class of bridged bicycle scaffolds in aqueous micellar



Scheme 27 Synthesis of quinoxaline, 1,4-benzoxazine and 1,4-benzothiazine scaffolds in CPB-micellar medium.





Scheme 30 (a) Construction of 2,8-dioxabicyclo[3.3.1]nona-3,6-dienes and (b) oxabicyclo[n.3.1]alkene frameworks in aqueous micellar medium.

3 Conclusion and outlook

Over the years, the science of organic synthesis has witnessed revolutionary strides in the establishment of new methods, strategies, and routes to gain access into the complex building blocks. However, one of the key concerns has been minimizing the use of volatile organic solvents, which directly impact our day-to-day lives. Among various strategies, one of the interesting strategies developed over the past couple of decades has been the micellar catalysis, which mimics nature's machinery of enzymatic synthesis. Though this field continues to attract the traction of organic chemists in aligning their science in tune with sustainable chemistry, it has also many challenges to overcome. As a result, some particular set of reactions involving C–C/C–heteroatom bond-forming reactions, multicomponent reactions, oxidations/reductions, rearrangements, cyclo-additions, fluorination reactions *etc.* have been successfully reported in aqueous micellar medium. From the past several years, a large number of heterocyclic compounds have been synthesized in a robust fashion using micellar catalysis. Applying this arena on reactions furnishing natural products and natural product building blocks is largely a silent field. One of the aims of writing this article is to compile the progress of micellar catalysis in various chemical transformations and the successful attempts are expected to encourage the new generation of chemists to align their chemistry towards green and sustainable fashion. Since the natural products synthesis is a daunting task involving the synthesis of complex building blocks and controlling the stereochemistry. Micellar chemistry

provides a window of opportunity to accomplish such goals with high degree of precision. Micellar catalysis not only enhances the reaction kinetics but selectivity of products also due to the compartmentalization effect. Together, these principles are expected to change the future course of organic synthesis with the discovery and development of new surfactant variants which are efficient to drive the tedious chemical transformations. Applicability of micellar catalysis is also expanding in pharmaceuticals at industrial level to chase the various drugs and their APIs in scalable quantities in water.⁸⁰ A continuous progress in this arena will have a positive impact on our environment and also enhance the longevity of the field of organic synthesis.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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