# "In Water" Syntheses of Heterocyclic Compounds

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**Abstract:** Recently an aqueous medium has attracted the interest of chemists for many organic synthesis, and sometimes, surprising discoveries have been made using water. Among the various organic reactions investigated in aqueous medium, the synthesis of heterocyclic compounds has been the most widely studied because heterocyclic compounds are rich sources of diverse physical, chemical, and biological properties. They are commonly used as templates to design biologically active agents in medicinal chemistry. Moreover, in the past 20 years, the drug-discovery process has undergone extraordinary changes, and high-throughput biological screening of potential drug candidates has led to an ever-increasing demand for novel drug, based on heterocyclic compounds. Noteworthy advantages were observed during the course of our study on "in water" synthesis of heterocyclic compounds. The established advantages of water as a solvent for reactions are: water is the most abundant and available resource on the planet and many biochemical processes occur in aqueous medium. This review is focussed on the use of water in the synthesis of heterocycles. Heterocycles that will be covered include acridine, benzothiazole, benzopyran, isoxazole, pyradazine, pyrazole, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, thiadiazole, triazole, xanthene, xanthone and others.

**Keywords:** Green chemistry, heterocycles, in water synthesis.

## INTRODUCTION

Green chemistry is a branch of chemistry, covering all chemical processes that are non-injurious to human health and are environmentally friendly, and its object is to prevent or at least reduce pollution at source [1].

Four main approaches, for synthesizing compounds in an environmentally friendly manner have been recently developed. One approach is to use water instead of organic solvent as reaction medium [2], second is to use no solvent at all [3], third approach is to replace stoichiometric amounts of metal reagents with small amounts of metal catalysts [4] and the fourth is to employ biosynthetic processes [5].

Among the alternative reaction media, water is one of the most intriguing due to its peculiar properties. Water is the most abundant and available molecule on the planet and many biochemical processes occur in aqueous medium. It has not been a favourite reaction medium for organic chemists, because its presence causes the decomposition of organomettalic reagents, which are used only in dry organic solvents. In fact, water has been generally used to work-up organic reactions and therefore it has been associated to a waste-production step and to the consequent obvious problems of cleaning-up water from reactants' residues. The probable reasons for this were: (i) that the low solubility of most organic compounds in water would probably be an obstacle to their reactivity, and (ii) the instability of many intermediates and catalysts in water.

Today, the scene has changed. The aqueous medium has captured the interest of organic chemists [6] and many other, sometimes as surprising, discoveries have been made used it [2]. It has been found that pericyclic, [7] condensation, [8,9] oxidation, [10] and reduction [10] reactions can be conducted efficiently in aqueous medium and that, in some cases, water is necessary to increase selectivity and reaction rate. Water-tolerant catalysts that allow organometallic reactions to be carried out in aqueous medium have been prepared [9-11]. Reactions previously thought impossible in water have become a reality today.

In 1980, Breslow's observations on the acceleration of some Diels–Alder reactions when carried out in water with respect to organic solvent [12] undoubtedly played a special role in the development of organic synthesis in aqueous media, but it must be mentioned that much earlier Diels–Alder reactions had been performed in water [13]. In 1931, Diels and Alder themselves [13*a*] used water as reaction medium in the cycloaddition of furan with maleic anhydride. In 1948, Woodward and Baer [13*b*] employed aqueous maleic acid as dienophile, and in 1973 the beneficial effect of aqueous medium on the reaction was also successfully investigated by Koning and Carlson [13*c*]. However, Breslow's kinetic work was the first that quantitatively showed the beneficial effects of water on the reactivity and selectivity of an organic reaction (for example the reaction of cyclopentadiene with butenone in water was accelerated by 740 times as compared to that performed in isooctane).

Many excellent reviews dealing with different aspects in this field have appeared, witnessing a large number of scientists presently involved in the study of water as reaction medium and its implications in different research areas [14].

There are many advantages using an aqueous reaction media. Among them, we wish to mention the possibility of recovery and reuse of the aqueous medium containing all the soluble species dissolved in it (catalysts and reactants), and the possibility of controlling the pH. This is of particular interest because it is than possible to influence the reactivity and solubility of the reactants, often allowing unique chemical behaviours to be displayed [15]. For example, it has been shown that salts such as $AlCl_3$, $TiCl_4$, $SnCl_4$ and $ZnCl_2$, believed to be decomposed by water, are on the contrary very effective catalysts provided that they are used under controlled pH conditions [16].

Fifteen years ago, the number of scientific publications concerning the use of ionic liquids, supercritical fluids, water or solvent-free conditions was very little.

Water is playing a major role as a solvent for the development of various heterocycles by replacing hazardous organic solvents. In this review we have tried to compile the "in water" synthesis of different class of heterocycles.

### Acridine

Wang *et al.* have described the one pot synthesis of unsymmetrical acridinediones using enaminones aldehydes and 1,3-cyclohexanedione under aqueous condition (Scheme **1**) [17]. To demonstrate the advantages of the reactions in water, selected reactions were conducted in organic solvents for comparison. The yields in organic solvents were generally lower than those in refluxing water due to the formation of byproducts.

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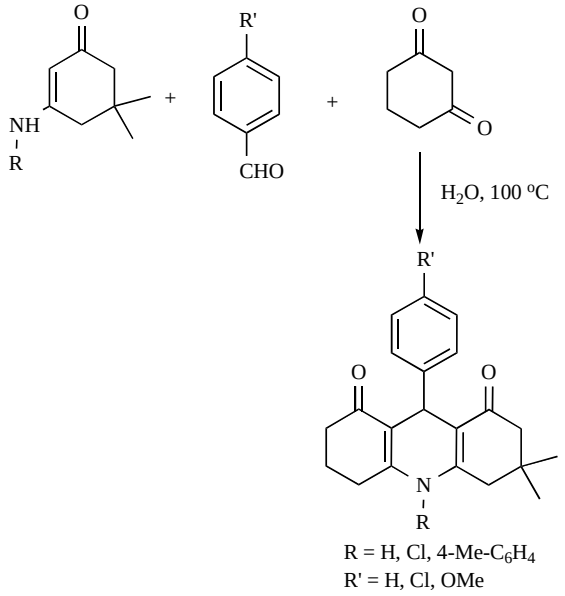
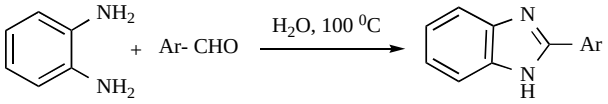



**Scheme 1.**

## Benzimidazole

A set of 2-aryl benzimidazoles were synthesized by Panda and Jain through a one pot condensation of *o*-phenylenediamines and aryl aldehydes in water with high yield (84-98%) and purity (Scheme **2**) [18].



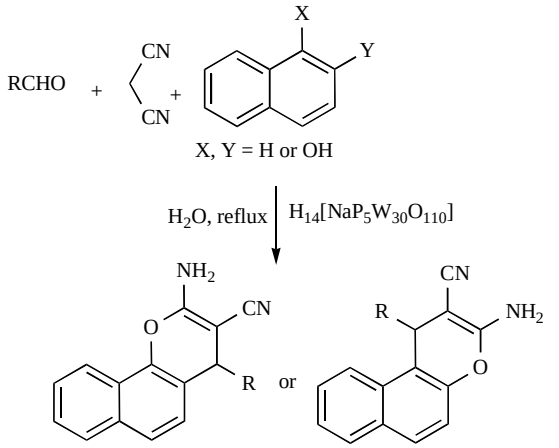

**Scheme 2.**

## Benzothiazole

A series of 2-substituted benzothiazole were synthesized in high yield in one pot reaction of aromatic, heteroaromatic, and styryl aldehydes with 2-aminothiophenol in water at 110ºC (Scheme **3**) [19] and the possible role of water was described in scheme **3a**.

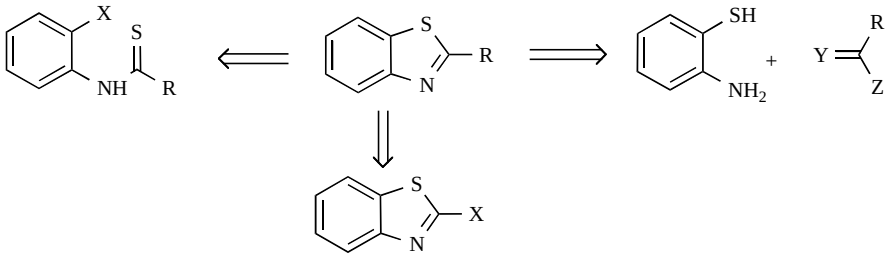
## Benzopyran

2-Amino-4*H*-chromenes were synthesized by Heravi *et al*. using Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$ as a green and reusable catalyst in water (Scheme **4**) [20]. The catalyst was used three times to promote the model reaction affording the corresponding chromene in 91, 89 and 87% yields, respectively, and with an excellent selectivity.

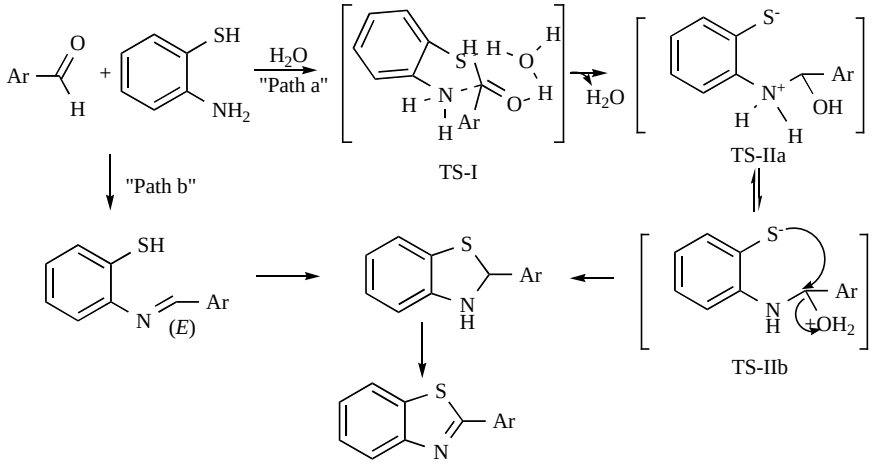



**Scheme 4.**

An efficient and convenient approach was described by Jin *et al.* to synthesize 2-amino-3-cyano-4-aryl-7,7-dimethyl-5-oxo-4*H*-

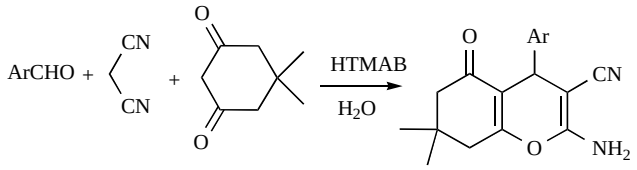



**Scheme 3.**



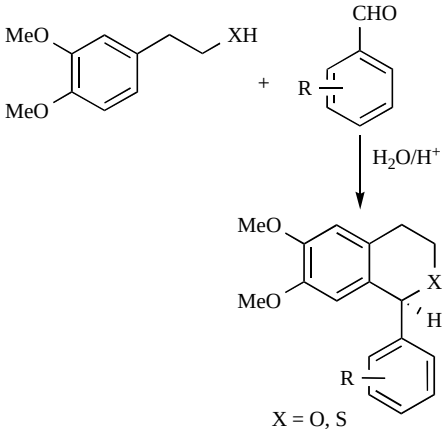

**Scheme 3a.**

5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives using hexadecyl trimethyl ammonium bromide (HTMAB) as the catalyst (10 mol%) (Scheme **5**) [21]. This is a one-pot procedure in aqueous media, which not only preserves the simplicity but also consistently gives the corresponding products in good to excellent yields.




**Scheme 5.**

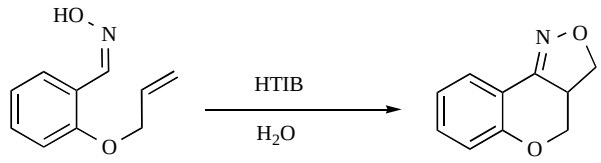
Saeed *et al.* have described an acid catalyzed oxa-Pictet–Spengler reaction in water leading to the synthesis of 1-aryl-6,7-dimethoxyisochromans (Scheme **6**) [22] in presence of a catalytic amount of *p*-toluenesulfonic acid or concentrated hydrochloric acid or sulphuric acid.




**Scheme 6.**

### Isoxazole

Raihan *et al.* have described an efficient and handy method for the synthesis of chromeno-isoxazole/isoxazolines in water, by [hydroxy(tosyloxy) iodo]benzene (HTIB) (Scheme **7**) and compared the yield with different organic solvents [23]. Using the same oxime and with a 10 mol% loading of HTIB, only a trace amount of the product was formed. An increase of the loading to 50 mol% resulted in a 35% yield of the expected product, and a trace amount of deoximination was observed. With an 1.1 equiv. of HTIB, the yield of the expected product reached maximum, but again with a minute amount of deoximination was observed.



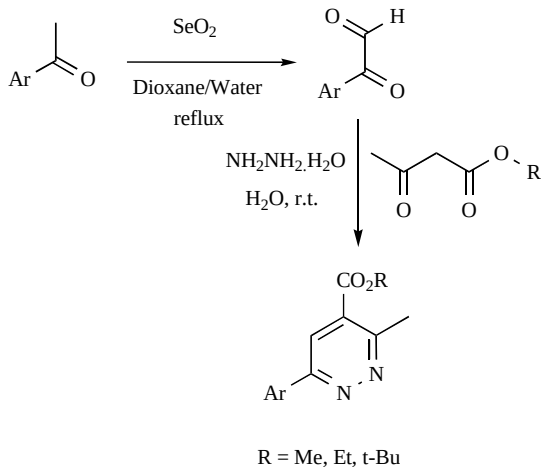

**Scheme 7.**

### Pyradazine

A series of new alkyl 6-aryl-3-methylpyridazine-4-carboxylates were efficiently synthesized by a three-component reaction of *β*-ketoesters with arylglyoxals in the presence of hydrazine hydrate in water at room temperature (Scheme **8**) [24].

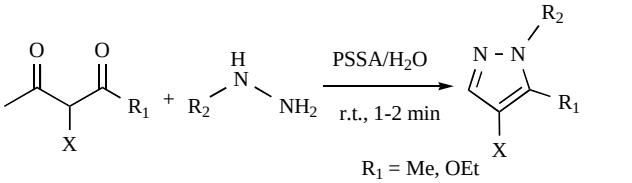
### Pyrazole

An expeditious aqua mediated synthesis of pyrazoles were carried out by condensation of hydrazines/hydrazides and diamines with various 1,3-diketones in the presence of polystyrene supported sulfonic acid (PSSA) [25] at room temperature in 1-2 min (Scheme




**Scheme 8.**

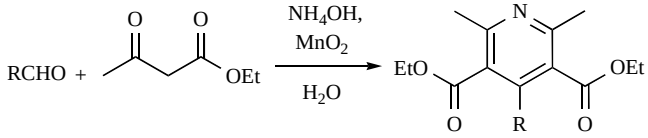
**9**). The reaction was optimize by the condensation of pentane-2,4-dione with phenyl hydrazine, using various acid catalysts: acetic acid, *p*-toluene sulfonic acid, and PSSA. Although reaction proceeds in each case, the yield and the rate of reaction was superior in the case of PSSA as compared to other catalyst.




**Scheme 9.**

### Pyridine

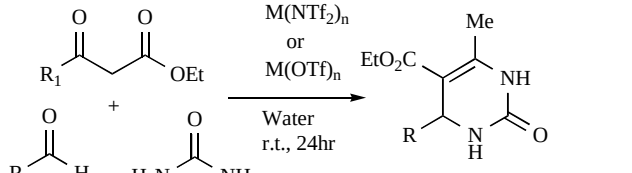
A series of 1,4-dihydropyridines were synthesized under refluxing condition in water by a reaction of aldehydes with ethylacetoacetate and ammonium acetate without any additives (Scheme **10**). Then manganese dioxide was added to the reaction system to obtain the corresponding oxidized pyridine derivatives in one pot under reflux conditions [26].




**Scheme 10.**

### Pyrimidine

Metal triflimides such as $Ni(NTf_2)_2$, $Cu(NTf_2)_2$ and $Yb(NTf_2)_3$ catalyzed the Biginelli reaction to afford 3,4-dihydropyrimidin-2(1*H*)-ones more efficiently in pure water at room temperature (Scheme **11**) [27]. $Ni(NTf_2)_2$ and $Yb(NTf_2)_3$ catalyzed the reaction



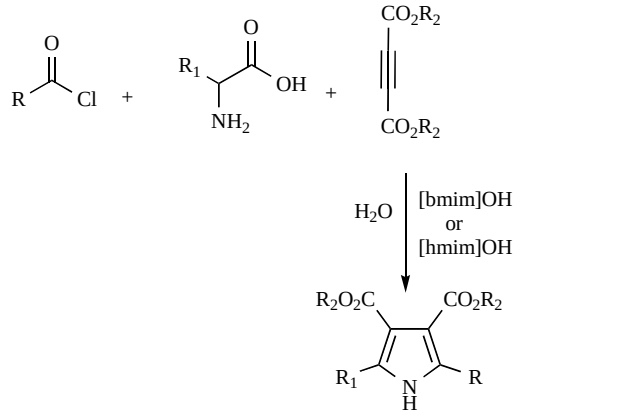

**Scheme 11.**

less effectively than $Cu(NTf_2)_2$. The Biginelli reaction of *p*- and *o*-nitrobenzaldehyde using $Cu(NTf_2)_2$, $Ni(NTf_2)_2$ and $Yb(NTf_2)_3$ with acid additives was failed probably due to the insolubility of these aldehydes in water.

The synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones in water in the presence of dodecyl sulfonic acid (DSA) was reported by Sharma *et al.* [28].

### Pyrrole

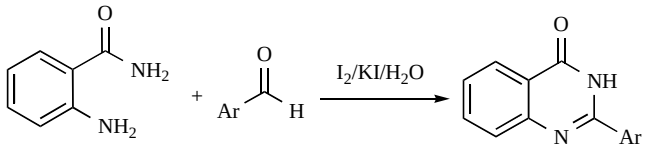
Tetrasubstituted pyrroles were synthesized by the three component condensation reaction of acid chlorides, dialkyl acetylenedicarboxylates, and amino acids in the presence of various ionic liquids (RTILs) as catalysts in water at room temperature (Scheme **12**) [29].




**Scheme 12.**

### Quinazoline

Bakavoli *et al*. have reported oxidative cyclocondensation of *o*-aminobenzamide with various aldehydes in water using $I_2$/KI as catalyst and oxidizing agent to obtain the corresponding quinazolin-4(3*H*)-ones (Scheme **13**) [30]. Quinazolin-4(3*H*)-one derivatives were previously prepared by thermolysis of 3-arylideneamine-1,2,3-benzotriazine- 4-ones in paraffin oil at 300°C or by condensation of aryl, alkyl and heteroaryl aldehydes in refluxing ethanol in the presence of $CuCl_2$, but both these methods require high-temperature reaction, low yield, long-reaction time as well as were not environment friendly.



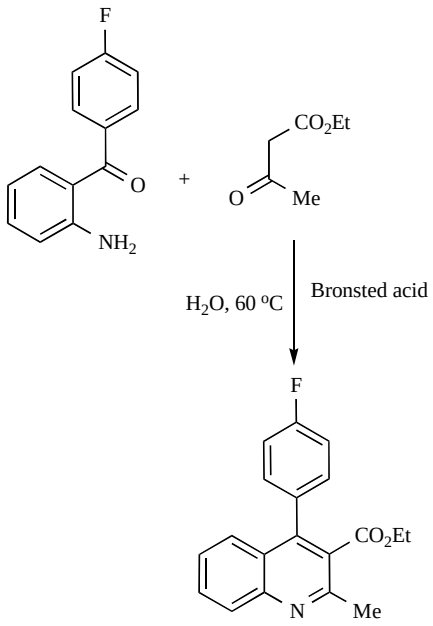
**Scheme 13.**

### Quinoline

Substituted quinoline derivatives were synthesized by a simple Friedlander reaction of 2-aminoarylketone or 2-aminoarylaldehyde with carbonyl compounds in the presence of hydrochloric acid utilizing water as the solvent (Scheme **14**) [31].

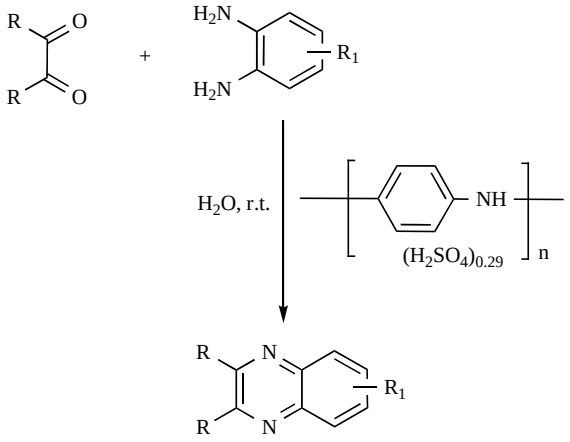
### Quinoxaline

Quinoxaline derivatives have been prepared in excellent yields by the condensation reaction between 1,2-dicarbonyl and aromatic diamine in water medium using small amount of polyaniline as catalyst (Scheme **15**). The rate of the reaction was enhanced using



**Scheme 14.**

sodium laurylsulfate (SLS) as surfactant. This methodology is very much useful in preparing quinoxaline derivatives even when the diamine and/or dicarbonyl compound are not soluble in water [32].



**Scheme 15.**

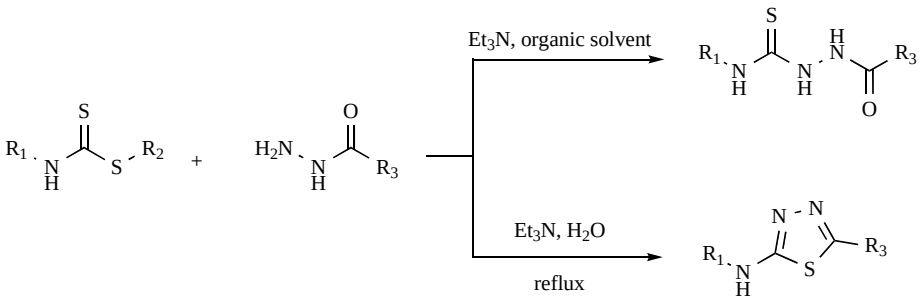
Cellulose sulfuric acid, as an efficient and environmentally friendly bio-supported proton source catalyst, was prepared and employed for the synthesis of quinoxaline derivatives *via* the condensation of 1,2-diketone with *o*-diamine in $H_2O$ or EtOH as a green solvent in relatively high yields at room temperature [33].

### Thiadiazole

Substituted 2-amino-1,3,4-thiadiazoles were synthesized by the reaction of dithiocarbamate with acid hydrazide in the presence of triethylamine or pyridine in water under refluxing condition (Scheme **16**). Where as the reaction, in high boiling solvents such as benzene, toluene, or DMF yields only hydrazinecarbo-thioamide [34].

### Triazole

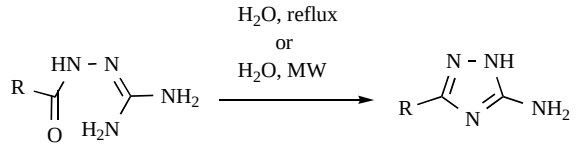
(Het)arylamidoguanidines, upon heating in water, underwent quantitative cyclocondensation with the elimination of a water molecule affording 3(5)-amino-5(3)-(het)aryl-1,2,4-triazoles (Scheme **17**). The reaction provided the products in excellent purity and did not require the presence of base or a catalyst. The solubility of the starting (het)arylamidoguanidines was found to be a limiting




$R_1$ = *n*-Bu, Ph, $PhCH_2$, 3,4-$Cl_2$-$C_6H_3$; $R_2$ = Et, $CH_2CH_2CN$; $R_3$ = Ph, $PhCH_2$, 4-Me-$C_6H_4$, 4-Pyridine

**Scheme 16.**

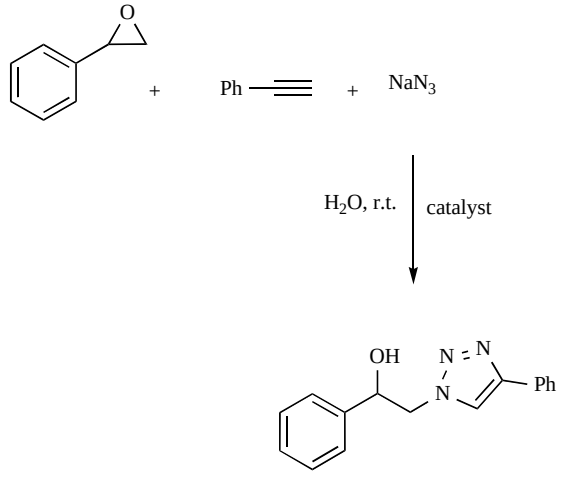
factor of the reaction. Excess of water or use of a co-solvent (ethanol) is required for some less soluble amidoguanidines. However, when ethanol is used as the solvent instead of water, the formation 3(5)-amino-5(3)-phenyl-1,2,4-triazole did not proceed to completion even after 3 days of heating under reflux [35].




R = Ph, 4-Me-$C_6H_4$, 4-F-$C_6H_4$, 2-Furyl, 2-Thienyl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl

**Scheme 17.**

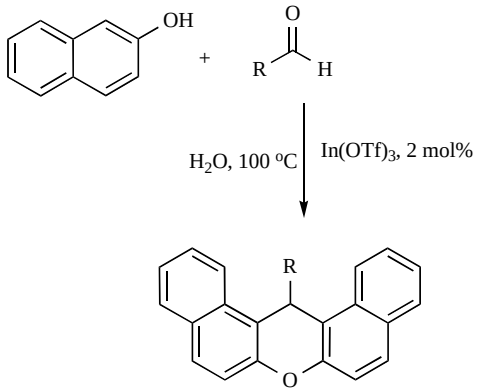
1-(2-Hydroxyethyl)-1*H*-1,2,3-triazole derivatives were prepared from oxiranes, $NaN_3$, and alkynes in $H_2O$ in the presence of catalytic amounts of a heterogeneous Cu(II) complex by way of a three component reaction. The reaction proceeds *via* the formation of 2-azido alcohols from the oxiranes and $NaN_3$ (Scheme **18**) [36].




**Scheme 18.**

## Xanthene

14-Alkyl or aryl-14*H*-dibenzo[*a,j*]xanthenes were prepared by condensation of 2-naphthol and aldehydes in the presence of a catalytic amount of indium(III) triflate (2 mol%) in water at 100°C (Scheme **19**) [37]. These compounds were previously prepared by using various catalysts such as silica sulfuric acid, Dowex-50W, $NH_4H_2PO_4$, sulfamic acid, $HClO_4.SiO_2$, cyanuric chloride, $Yb(OTf)_3$, alum, and $BF_3.SiO_2$. However, the above-mentioned catalysts have several disadvantages because they are corrosive, toxic, or volatile and generate large amounts of waste material.

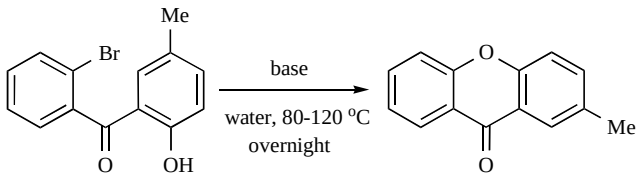



R = Ph, 4-Me-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 2-Pyridyl, Cyclohexyl, $(CH_3)_2CH$, $CH_3CH_2CH_2$

**Scheme 19.**

## Xanthone

Xanthones were prepared by unusual displacement of bromine through nucleophilic aromatic substitution reactions of 2-bromobenzophenone in presence of either 2 equiv. of KOH or one equiv. of $Na^tOBu$ in water under heating condition (Scheme **20**) [38].

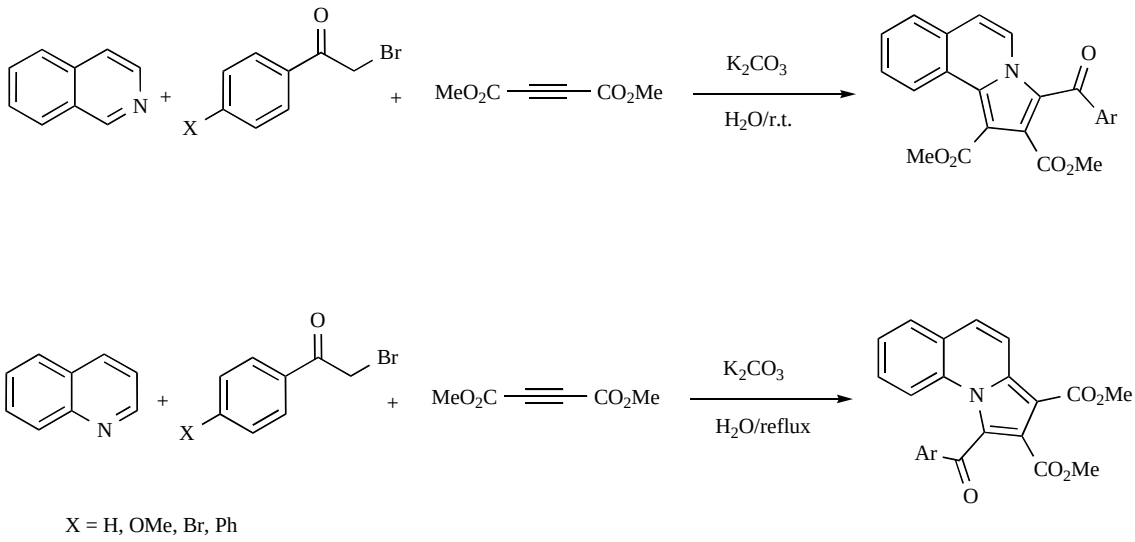



**Scheme 20.**

Along with various classes of basic heretocycles, water also plays an important role in the synthesis of fused ring and complex heterocyclic systems. These types of compounds are summarized under miscellaneous category.

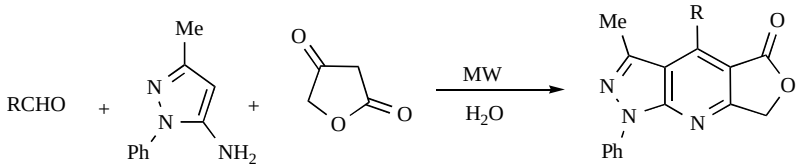
## Miscellaneous

Pyrrolo[2,1-*a*]isoquinolines and pyrrolo[1,2-*a*]quinolines in good to excellent yields has been reported, using quinoline or isoquinoline, phenacylbromide derivatives and activated alkynes in aqueous medium (Scheme **21**) [39]. No reaction was observed at room temperature with quinoline ylides and all of the reactions were carried out at refluxing condition. However, isoquinoline ylides produced the corresponding products in good to excellent yields at room temperature. To increase the efficiency of this process, investigations were carried out for the development of a one-pot reaction in which the salt and the ylide could be generated *in situ*, in water, from the readily available starting materials.




**Scheme 21.**

A series of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine analogues of podophylloxin were synthesized *via* three component reaction of aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and tetronic acid in water under microwave irradiation without using any catalyst (Scheme **22**) [40].

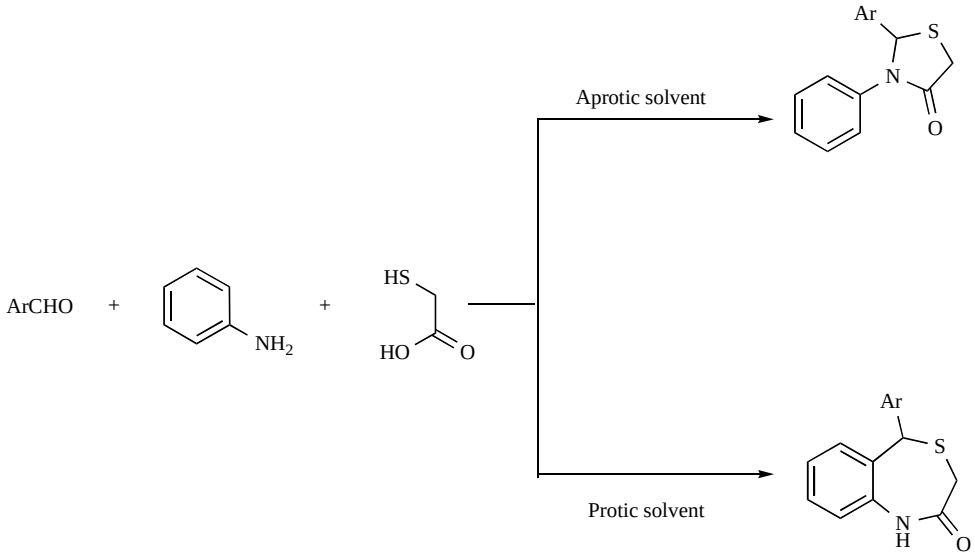



**Scheme 22.**

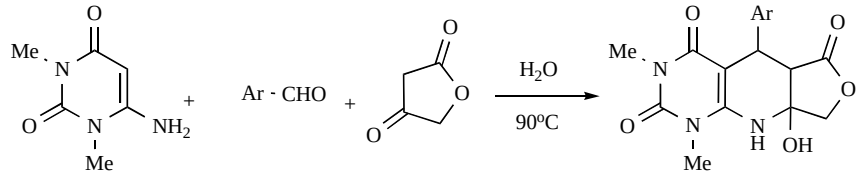
Benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-ones were synthesized *via* a microwave-assisted chemoselective multi-component reaction in aqueous media (Scheme **23**) [41]. When the reaction was carried out in aprotic solvents such as benzene, dichloromethane, DMF and THF it afforded thiazolidinones in excellent yields. Interestingly, the use of protic solvents such as glycol, ethanol, glacial acetic acid (HOAc) and water gave low to moderate yields of the product benzo[*e*][1,4]thiazepin-2(1*H*,3*H*,5*H*)-ones. The best protic solvent found was water.

A series of furo[2′,1′:5,6]pyrido[2,3-*d*]pyrimidine derivatives were synthesized by Shi and Yao *via* the three-component reaction of an aldehyde, tetronic acid, and 6-amino-1,3-dimethyl-pyrimidine-2,4-dione in aqueous media without the use of catalyst (Scheme **24**). This protocol has the advantages of better yields, less cost, reduced environmental impact, and convenient procedure [42].

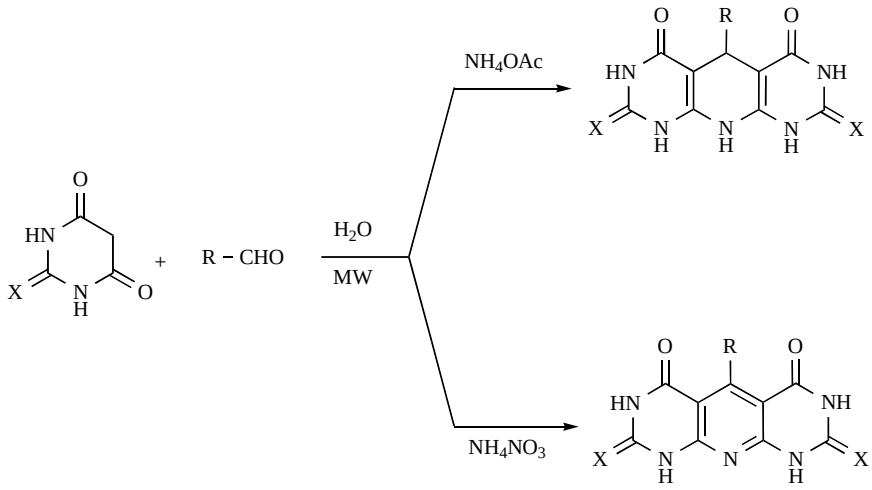
Dipyrimidine-fused pyridine derivatives were synthesized using 1,3-diketone, aldehyde, different ammonium salts, and water as the solvent (Scheme **25**). Aromatization was observed when




**Scheme 23.**



**Scheme 24.**

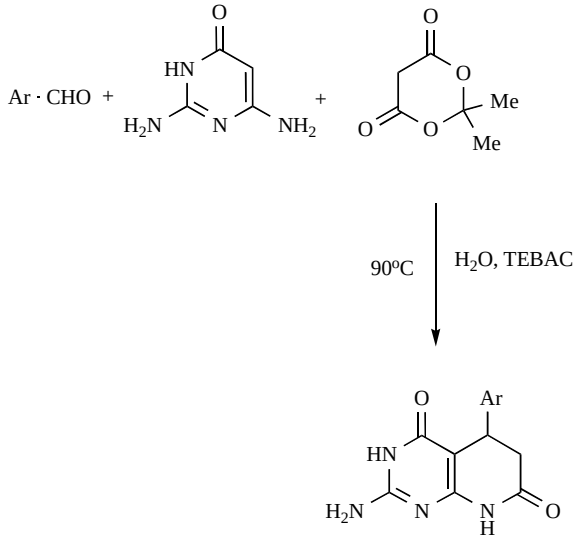


R = Ph, 2-HO-$C_6H_4$, Piperonyl, Thienyl, 2-Cl-Quinolinyl

**Scheme 25.**

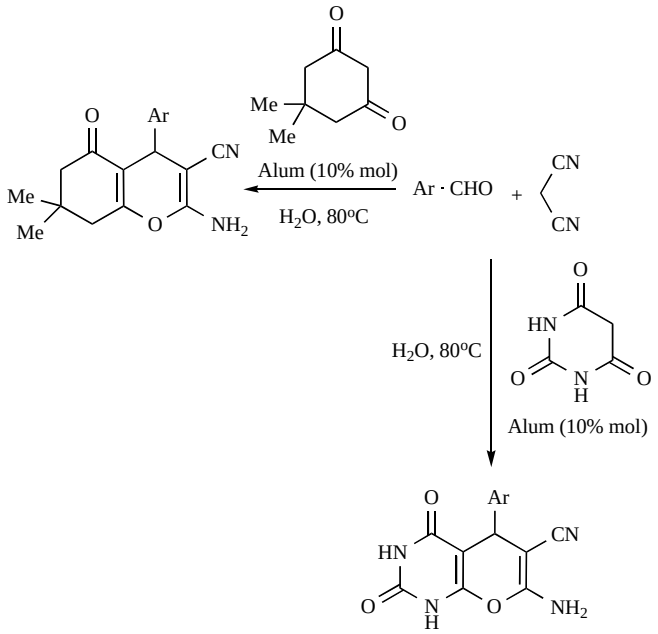
ammonium nitrate was used as the source of nitrogen, and thus, dipyrimidine-fused pyridine derivatives were synthesized in one-pot synthetic procedure. This environmentally benign procedure leads to high yield of products (80%–90%) in a single step, with greater purity using water as the solvent [43].

A series of 2-amino-5-aryl-5,6-dihydropyrido[2,3-d]pyrimidine-4,7(3*H*,8*H*)-dione derivatives were synthesized *via* the three-component reaction of aromatic aldehyde, 2,6-diaminopyrimidine-4(3*H*)-one and Meldrum's acid in water in the presence of triethylbenzylammonium chloride (TEBAC) (Scheme **26**). This protocol has the advantages of easier work-up, milder reaction conditions, and environmentally benign procedure [44].



**Scheme 26.**

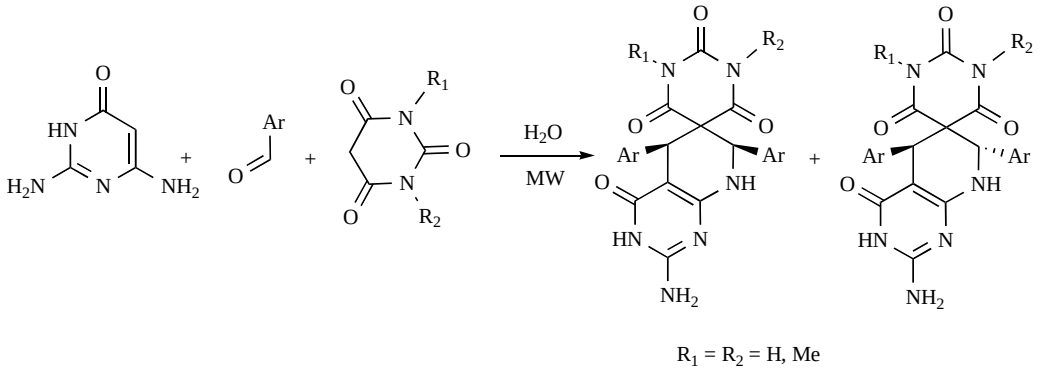
Tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone derivatives were synthesized efficiently *via* a domino Knoevenagel-cyclocondensation reaction using $KAl(SO_4)_2.12H_2O$ (alum) as a catalyst in water (Scheme **27**). Green media, lack of toxicity, short reaction times, easy work-up and high yields are some advantages of this method [45].



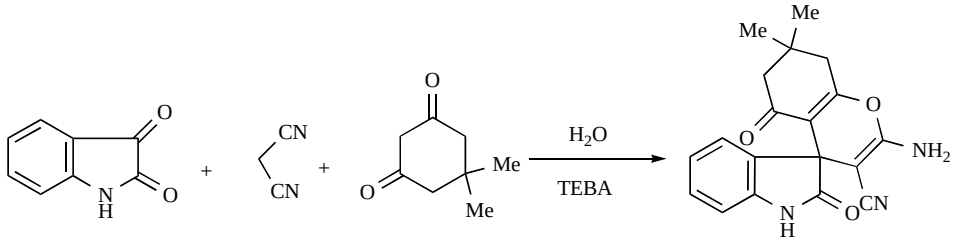
**Scheme 27.**

A highly diastereoselective domino reaction of 2,6-diaminopyrimidine-4-one with structurally diverse aryl aldehydes and various barbituric acids in water under microwave irradiation was described (Scheme **28**). The products are 6-spiro-substituted pyrido[2,3-*d*]pyrimidines with high diastereoselectivities (up to 99: 1) in which the major diastereomer bears a *cis* relationship between substituents at the 5- and 7-positions [46].

A simple and efficient one-pot three-component synthesis of the biologically important spirooxindoles scaffold was carried out by the reaction of isatin, activated methylene reagent, and 1,3-



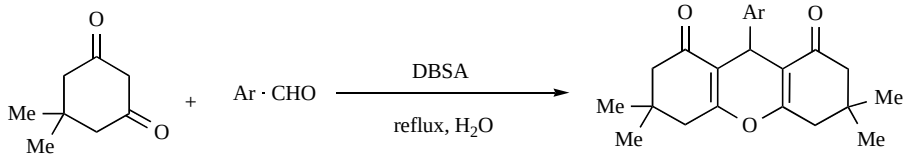

**Scheme 28.**




**Scheme 29.**

dicarbonyl compounds in aqueous medium in presence of triethylbenzylammonium chloride (TEBA) (Scheme **29**) [47]. The reaction was carried in the absence/presence of several other additives. It was found that when the reaction was carried out without any additives, the product was obtained in poor yield. Some bases or acids such as $NaHCO_3$, $K_2CO_3$, and PTSA can push the reaction forward with moderate yields. When surfactants, for example, TBAB (tetrabutylammonium bromide), SDS (sodium dodecyl sulfate), and CTAC (cetyl trimethyl ammonium chloride) were used in this reaction, the yields of products were improved. The best result (up to 94%) was obtained when TEBA was used.

An efficient and convenient approach to the synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxo-octahydroxanthene derivatives using *p*-dodecylbenezenesulfonic acid (DBSA) as the catalyst (10 mol%) was described by Jin *et al.* (Scheme **30**) [48]. The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. Increasing the amount of the catalyst to 5 mol%, 10 mol%, and 15 mol% results in increasing the reaction yields. Use of just 10 mol% DBSA at reflux in water is sufficient to push the reaction forward.



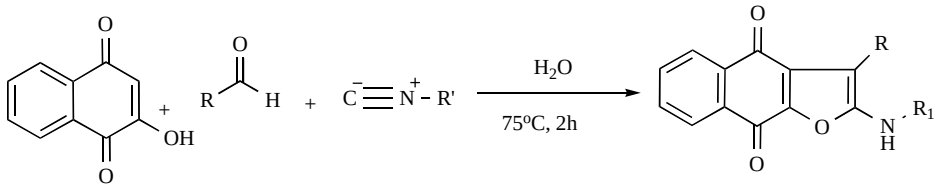

**Scheme 30.**

An efficient and clean green synthesis of highly substituted linear naphtho[2,3-*b*]-furan-4,9-dione derivatives, starting from 2-hydroxynaphthalene-1,4-dione, alkyl isocyanides and a variety of aldehydes, is described (Scheme **31**). This new method provides the first example of an efficient regioselective synthetic method for the synthesis of linear naphtho[2,3-*b*]- furan-4,9-dione ring systems by formation of three bonds [49].

A series of furo[3,4-*b*][4,7]phenanthroline and indeno[2,1-*b*][4,7] phenanthroline derivatives were synthesized *via* a three-component reaction of aromatic aldehydes, 6-aminoquinoline and either tetronic acid or 1,3-indanedione in water, under microwave irradiation without use of any catalyst (Scheme **32**) [50].

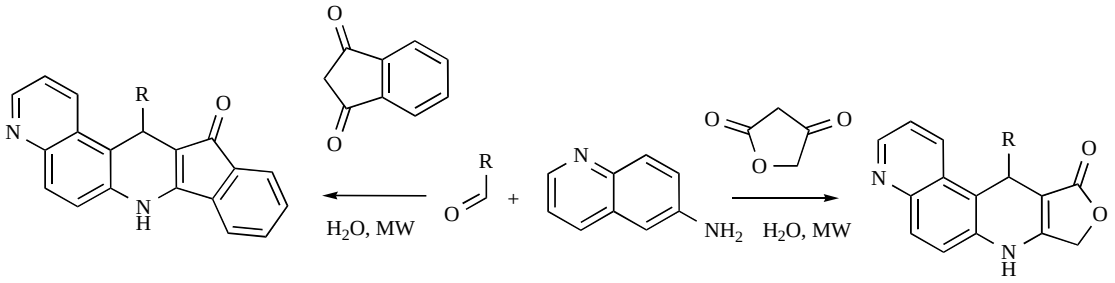
Silica functionalized Cu(I) is reported by Shamim *et al.* as a green and recyclable heterogeneous catalyst for the regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles *via* Huisgen 1,3-dipolar cycloaddition reaction between terminal alkynes, benzyl/allyl/alkyl halides and $NaN_3$ in water at room temperature (Scheme **33**) [51].

The reaction of oxiranes with carbon disulfide for the preparation of cyclic dithiocarbonates was carried out in water with



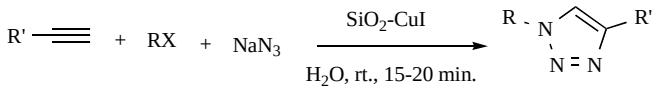

R = Me, Propyl, Ph, 4-$NO_2$-$C_6H_4$, 3-HO-$C_6H_4$, 2,5-di-OMe-$C_6H_3$
$R_1$ = Cyclohexyl, *tert*-Butyl, *tert*-Octyl

**Scheme 31.**

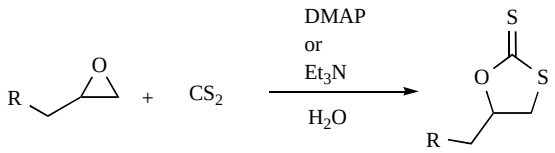



**Scheme 32.**

catalytic amount of an organic base [52]. For this purpose, different Lewis bases such as $Et_3N$, DMAP, DABCO, and DBU were examined, and it was found that DMAP and $Et_3N$ (10 mol %) gave the best results for the preparation of cyclic dithiocarbonates (Scheme **34**).

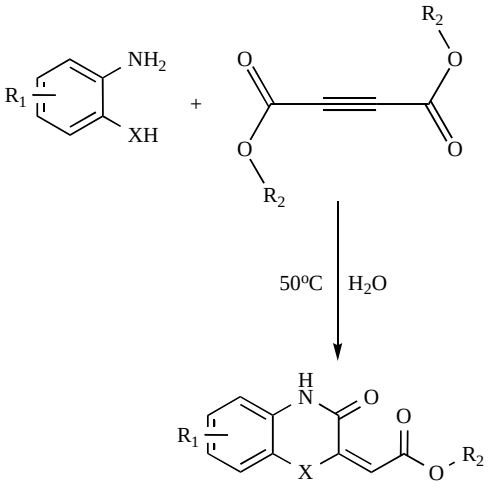



**Scheme 33.**




**Scheme 34.**

A fast and efficient protocol which is associated with readily available starting materials, mild conditions, excellent yields (91%-97%), and a broad range of the products in synthetic chemistry, was established for synthesis of quinoxaline, benzoxazine, and benzothiazine derivatives in water under catalyst-free conditions at 50°C (Scheme **35**) [53].




X = O, S, NH
$R_1$ = Cl, $NO_2$, *t*-Bu
$R_2$ = Me, Et

**Scheme 35.**

In conclusion, this article has attempted to summarize key discoveries in this area as well as some of the most promising new organic reactions in aqueous medium. We can see that types of reactions that can be carried out in water are as diverse as those in nonaqueous conditions. Most importantly, completely new reactivities have been discovered by using water as a solvent. Thus, organic synthesis in water can significantly reduce the number of steps when designed properly. Ultimately, the combination of shortening synthetic routes, increasing product selectivity, and reducing volatile organic consumption will certainly provide economical, health, and environmental benefits to the mankind.

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