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## Original article

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Kobra Nikoofar, Fatemeh Molaei Yielzoleh

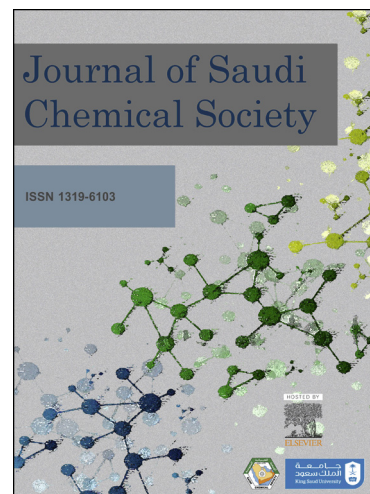
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**A concise study on dimedone: a versatile molecule in multi-component reactions, an outlook to the green reaction media**

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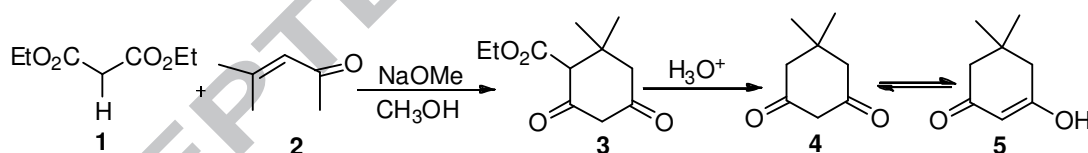
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**Abstract:** Dimedone is an interesting and versatile motif in most organic transformations. Its white to light yellow crystals have been utilized as substrate in wide range of organic reactions including multi-component transformations. The notability of dimedone is due to the acidic property of its methylene group which is in equilibrium with its tautomeric enol form. This phenomena permit dimedone to be utilized in several kinds of organic reactions eventuated to several organic molecules with potent pharmaceutical exclusivity. The mentioned nature of dimeodne in addition with its low toxicity, easily accessibility and handling, moisture stability, and low cost make it interesting for organic chemists. During the last decades, perfuming an organic transformation based on green chemistry rules, is in demand. In this review the reactions of dimedone has been focused with an outlook to the solvent of media. Each section has been subdivided respect to the temperature of the transformations. All categorizations has been accomplished to the green media. The authors has also calculated the atom economy of each reaction on behalf of green chemistry concept.

**Keywords:** Dimedone; multi-component reactions; solvent-free; organic transformations; aqueous media

## 1. Introduction

5,5-Dimethylcyclohexane-1,3-dione (**4**) is a cyclic diketone used in organic chemistry. These white to light yellow crystals have also named dimedone, cyclomethone, 5,5-dimethyl-1,3-cyclohexanedione, dimethyldihydroresorcinol, and methone.  $C_8H_{12}O_2$  (Mw = 140.17968 g/mol) with the melting point of 147-150 °C (420-423 K), is stable under ambient conditions and soluble in water, as well as ethanol and methanol, and inorganic solvents. It could be prepared from diethyl malonate (**1**) and mesityl oxide (**2**) [1]. It is a safe compound which didn't show any hazardous during usage (LD50 oral  $\geq$  5000 mg/kg). Dimedone is in equilibrium with its tautomeric enol form **5** (keto/ enol: 2/ 1) in chloroform (Scheme 1) [2], the hydrogen bonding between the enolic structure caused its crystalline appearance [3].



**Scheme 1** Preparation of dimedone and its tautomerization

Dimedone and its derivatives possessed many biological properties such as anticarcinogenic [4], antioxidant [5-6], antihistaminic [7], and anticoagulant [8].

During its oxidation process the chemiluminescence have been observed, which belongs to 4-peroxydimedone radicals that has been obtained from the first step oxidation. [9]. Other utilities include applications in colorimetry, crystallography, luminescence, and spectrophotometric analysis. It can also be used for chemistry involving organic compounds

of low electrical resistance [10]. The mixed solution of dimedone and orthophosphoric acid can be used as a spraying reagent for selective detection of keto sugars by paper chromatography [11].

Green chemistry, also called sustainable chemistry, that possessed 12 basically rules, is an area that focused on processes designation in order to minimize the use and generation of hazardous substances. In reality, it discussed about the synthetic methods to prevent pollution and reducing consumption of non-renewable resources [12-14], minimizing the amount of toxic waste and by-products [15]. In addition ecological consideration must be apportioned. Hence, performing the reaction in the absence of non-environmental organic solvents is one of the goals that participated with green chemistry, as they usually used in large quantities. This idea could be proved through doing the reaction in a solvent-free media and/ or accomplishing it in water [16].

In this review the applications of dimedone, as a versatile framework, in green organic reactions has been investigated. The authors divided the outline into two parts: a) solvent-free conditions, and b) water media. Each part has been subdivided to the room temperature reactions and heat-based transformations. Besides the calculation of atom economy (ae) of each reaction, they hoped this article displayed a helpful map to the green chemistry of dimedone-based synthesis.

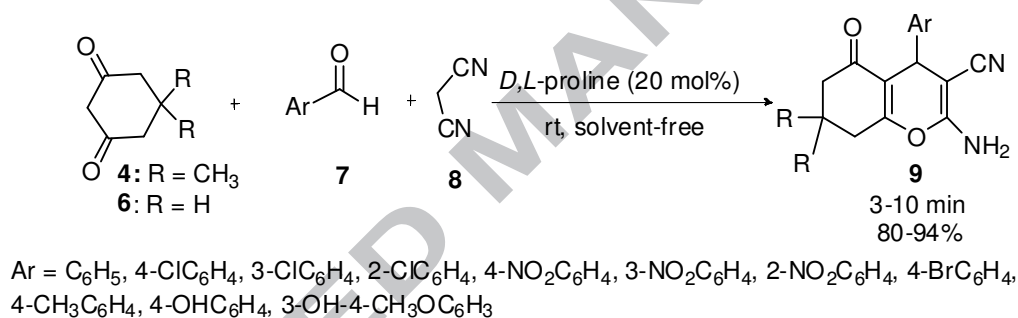
## **2. Reaction of dimedones under solvent-free conditions**

In a solvent-free or solid state situation, the reaction progressed alone in the absence of any solvent. In this case, in addition to the room temperature, thermal process or irradiation with UV, microwave or ultrasound could be employed, as an auxiliary, to accelerate the reaction. Solvent-free procedure have some advantages such as reducing the pollution, low cost, simplification of experimental and work up procedure, high yields of products due to

avoiding by-products formation, and short time of transformation because of straight correlation of the substrate [17].

### 2.1. Reaction of dimedones under solvent-free conditions at room temperature

Guo and co-workers reported in 2007 the three-component one-pot reaction of dimedone (**4**)/1,3-cyclohexanedione (**6**), aromatic aldehydes (**7**), and malononitrile (**8**) in the presence of *D,L*-proline under solvent-free conditions at ambient temperature to produce 2-amino-3-cycano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[*b*]pyrans (**9**) (Scheme 2) [18]. The reaction proceeded cleanly at room temperature to afford the products (ae = 94%) in good yields.



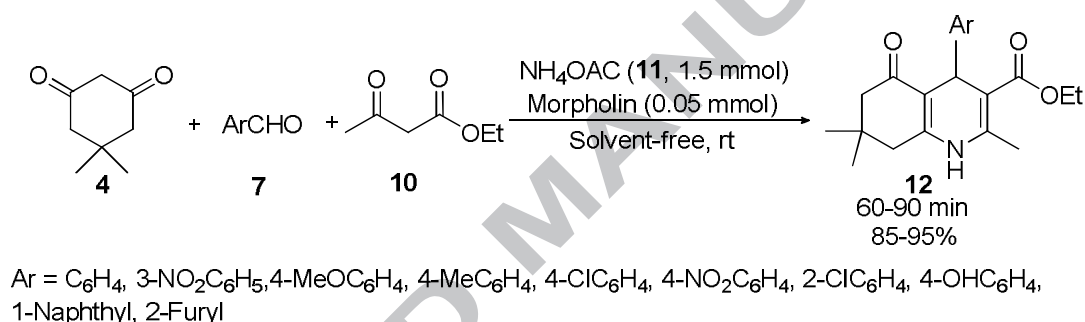
**Scheme 2.** Synthesis of 2-amino-3-cycano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[*b*]pyrans.

Naimi-Jamal et al. reported the synthesis of **9** under solvent-free kneading ball-milling conditions by sodium carbonate (10 mol%) within 10-40 min by more than 99% yield. Different aromatic aldehydes has been utilized successfully [19]. Red sea sand (0.5 g) under microwave irradiating (200 W) is another catalytic system that gained **9** within 3-5 min by 79-95%, which was introduced by Abd El-Rahman and co-workers in 2014 [20].

2-Hydroxy ethylammonium formate ([H<sub>3</sub>N<sup>+</sup>-CH<sub>2</sub>CH<sub>2</sub>-OH][HCOO<sup>-</sup>], 0.27 mmol) could also catalysed this reaction within 2-10 min in moderate 43-86% yields [21]. In 2013

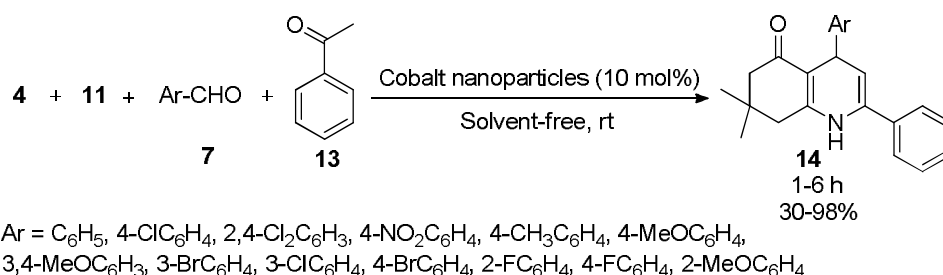
Pitchumani group represented per-6-amino- $\beta$ -cyclodextrin (per-6-NH<sub>2</sub>- $\beta$ -CD, 0.09 mmol), as a reusable catalyst, to accelerate **9** formation within very short 1-7 min period via grinding method utilizing a mortar and pestle [22].

Heravi and co-workers synthesized a series of unsymmetrical 1,4-dihydropyridines (**12**) via a sequential Hantzsch condensation of **4**, **7**, ethyl acetoacetate (**10**), and ammonium acetate (**11**) in the presence of morpholine at room temperature under solvent-free conditions (Scheme 3) [23]. The atom economy of this transformation is 90%. 10-Substituted 1,4-dihydropyridines (1,4-DHPs) are analogues of NADH coenzymes and an important class of drugs [24].



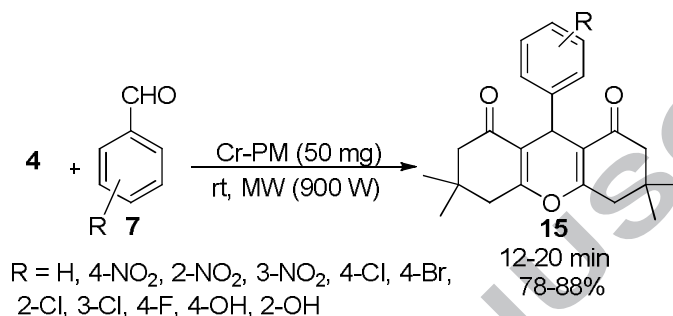
**Scheme 3.** 10-Substituted 1,4-dihydropyridines (1,4-DHPs) preparation.

Safari and co-workers demonstrated a straightforward and general method for the synthesis of C5-unsubstituted 1,4-dihydropyridines (**14**) via the reaction of **4**, **7**, **11**, and acetophenone (**13**) in the presence of cobalt nanoparticles, as a heterogeneous and eco-friendly catalyst with high catalytic activity, at room temperature under solvent-free conditions (ae = 74%) (Scheme 4) [29].

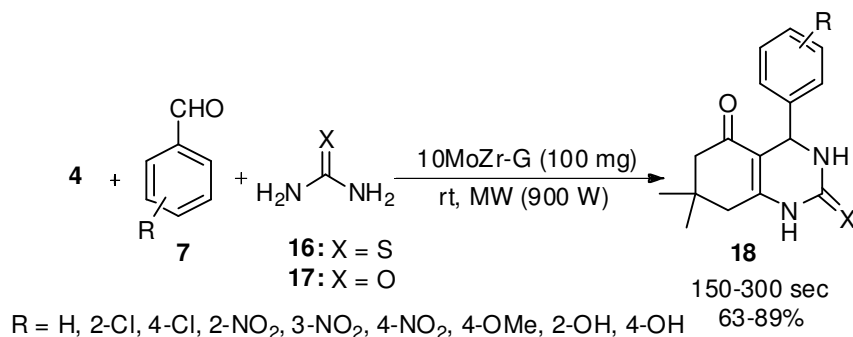


**Scheme 4.** Synthesis of C5-unsubstituted 1,4-DHPs.

Kar et al. developed one-pot synthesis of octahydroxanthenes (**15**) using chromia-pillared montmorillonite (Cr-PM) at room temperature under microwave irradiation through the condensation of **4** and **7** in a 2: 1 molar ratio (ae = 91%) (Scheme 5) [30].

**Scheme 5.** Synthesis of octahydroxanthenes.

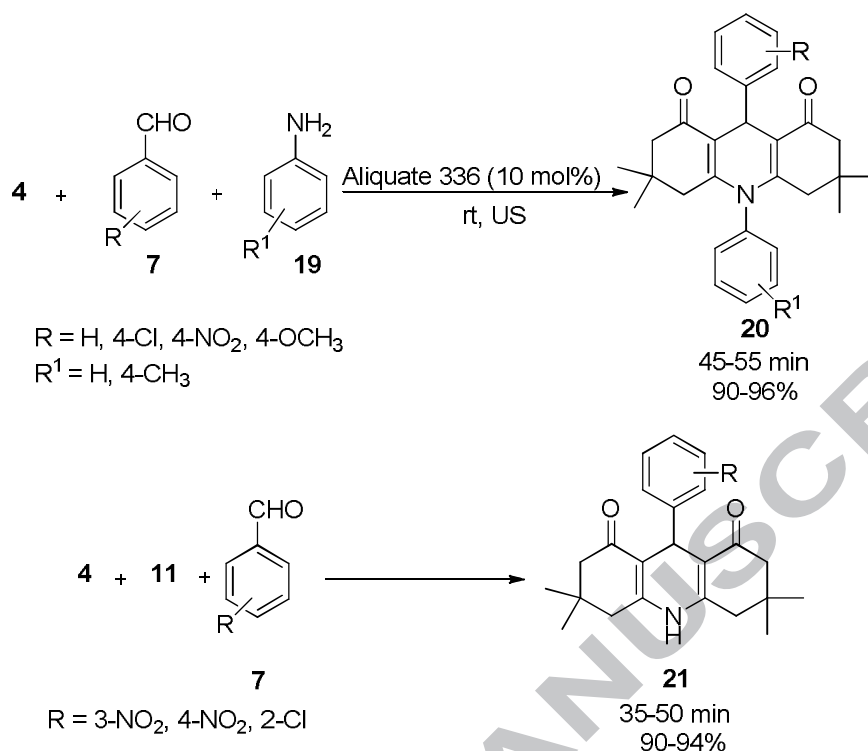
Mishra and Samantaray in 2011 prepared MoO<sub>3</sub>-ZrO<sub>2</sub> nanocomposite oxide (MoO<sub>3</sub> (10 mol%)-ZrO<sub>2</sub>, which named 10MoZr-G) via a solution combustion method and utilized it as an efficient and environmentally benign catalyst for the synthesis of octahydroquinazolinones (**18**), ae = 88%, through the multi-component condensation reaction of **4**, **7**, and urea (**16**)/ thiourea (**17**) by 900 W power of microwaves (Scheme 6) [31]. The same reaction has been performed in refluxing water in long period (4-10 h) with low to moderate yield of 66-82%.

**Scheme 6.** Octahydroquinazolinones preparation.

Badadhe et al. [32] has also done microwave-assisted (960 W) thiamine hydrochloride (VB<sub>1</sub>, 10 mol%) catalysed three-component Biginelli condensation of dimedone (**4**), **16/ 17**, and substituted aromatic aldehydes (**7**) for the synthesis of **18** in the absence of solvent within 2.5-16 min by 82-93% yield. Lanthanum oxide (La<sub>2</sub>O<sub>3</sub>, 10 mol%) is another catalytic system to prepare **18** under microwave irradiation (480 W) within 32-80 sec by 90-98% yield. In addition with aromatic aldehydes phenylethenal has also performed the reaction successfully [33].

In 2013 Kumar et al. described an ultrasound-assisted (with a frequency of 40 KHz), clean, and efficient protocol to get some classes of acridinediones, including *N*-aryl-tetrahydroacridine-1,8 (2*H*,5*H*,9*H*,10*H*)-diones (**20**) and tetrahydroacridine-1,8 (2*H*,5*H*,9*H*,10*H*)-diones (**21**) from the multi-component reaction of aromatic aldehydes (**7**), **4**, and amines (**19**) or ammonium acetate (**11**) in the presence of methyltrioctylammonium chloride (Aliquate 336) at room temperature respectively (Scheme 7) [34]. Acridine diones have attracted keen interest because of their usage as DNA-binding moieties and DNA-intercalating anticancer drugs [35]. The atom economy of the obtained products are 89% and 75% respectively.

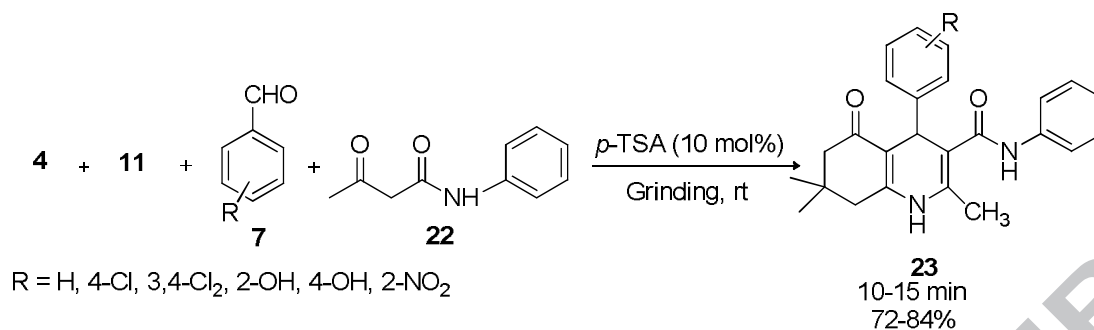




**Scheme 7.** Route of acridinediones formation.

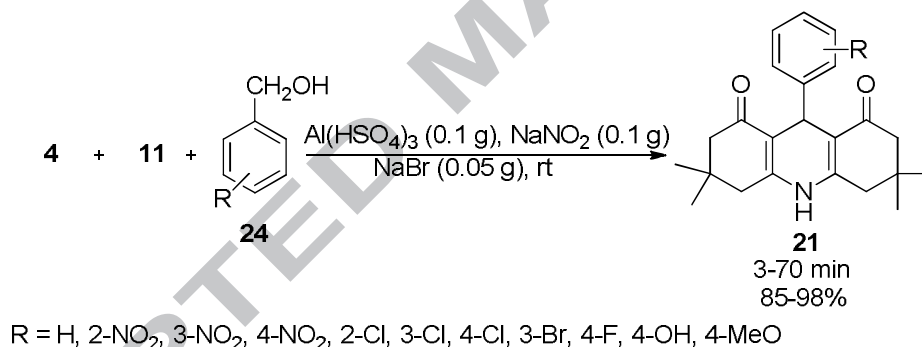
1-Methylimidazolium tricyanomethanide ([HMIM]C(CN)<sub>3</sub>, 0.5 mol%) as a nanostructured molten salt (NMS) catalyst at room temperature is another catalyst to prepare **20/21** within 5-35 min by 90-98% [36].

A facile and efficient method have developed for processing a variety of hexahydroquinolines (**23**) by Ahmed and co-workers through the four-component condensation reactions of **7**, **4**, acetoacetanilide (**22**), and **11** via an improved grindstone reaction catalysed by *p*-TSA (ae = 77%, Scheme 8) [37]. All the designed compounds showed binding affinities as well as interactions with all the crucial amino acid residues on par with the reference standard (Fluoxetine). Compounds which were predicted to have good binding affinity (docking score) were considered for further MDA and histological studies.



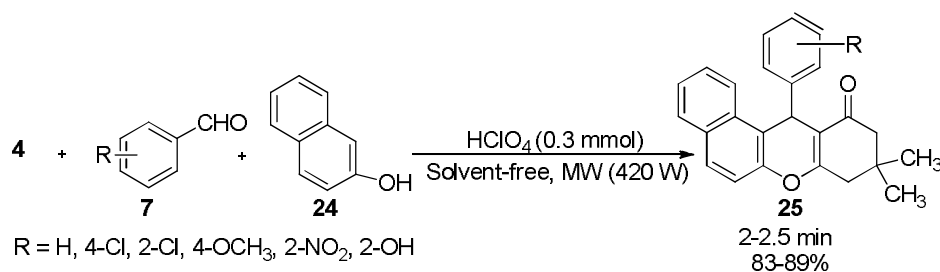
**Scheme 8.** Hexahydroquinolines.

Another interesting route to obtain **21** has been reported via the pseudo-four-component condensation of benzyl alcohols (**24**), dimedone, and ammonium acetate in the presence of  $\text{Al}(\text{HSO}_4)_3$  (0.1 g),  $\text{NaNO}_2$  (0.1 g), and  $\text{NaBr}$  (0.05 g) at room temperature under solvent-free conditions (ae = 75%, Scheme 9) [38].



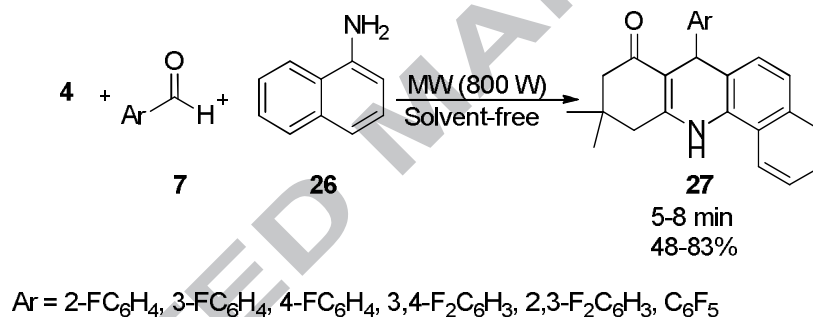
**Scheme 9.** Route of acridinedione formation from benzyl alcohols.

Gulam Mohammed and co-workers [39] described microwave promoted perchloric acid catalysed one pot synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]-xanthen-11-one derivatives (**26**) by condensation of several substituted benzaldehydes (**7**),  $\beta$ -naphthol (**25**), and **4** at ambient temperature under solvent-free conditions (ae = 91%, Scheme 10). Xanthenes structural motifs have found as antagonists for paralyzing the action of zoxazolamine [40].



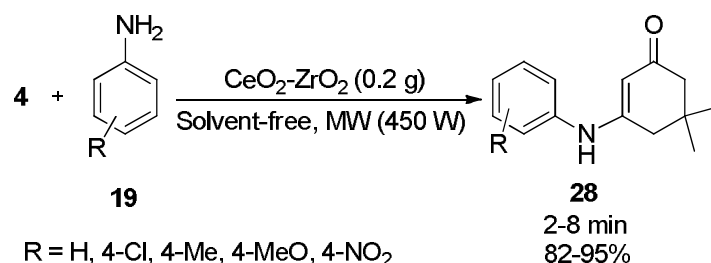
**Scheme 10.** 12-Aryl-8,9,10,12-tetrahydrobenzo[a]-xanthen-11-ones.

A facile route to prepare fluorine-containing polyhydrobenzoacridines (**27**) was accomplished by a three-component catalyst-free coupling of fluorinated aldehydes (**7**),  $\alpha$ -naphthylamine (**26**), and **4** under microwave irradiation at room temperature (ae = 91%, Scheme 11) [41].



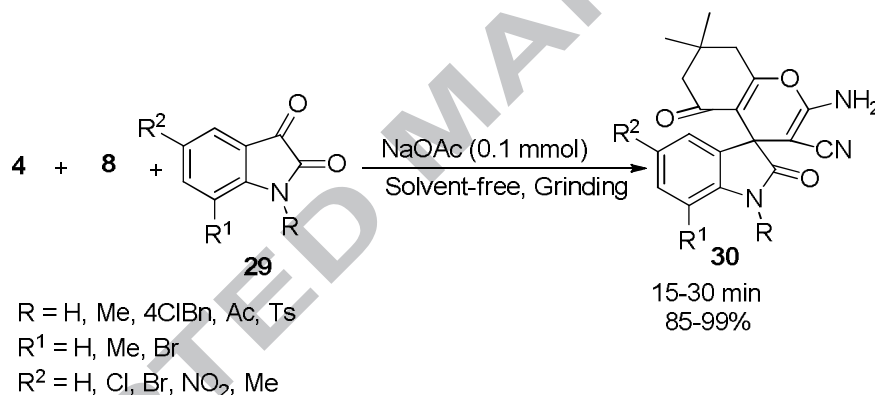
**Scheme 11.** Polyhydrobenzoacridines.

Rathod et al. [42] in 2014 explained synthesis of  $\beta$ -enaminones (**28**) by condensation of various anilines (**19**) with **4** in the presence of the binary oxides CeO<sub>2</sub>-ZrO<sub>2</sub> (1:1) in microwave which provided the products in excellent yields with ae = 92% (Scheme 12). Besides the aniline derivatives, benzyl amine and  $\beta$ -naphthyl amine have also performed the reaction prosperously.



**Scheme 12.** Preparation of  $\beta$ -enaminones.

2-Amino-7,7-dimethyl-20,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitriles (**30**) has been obtained by Elinson and co-workers via the solvent-free sodium acetate catalysed multi-component reaction of isatins (**29**), malononitrile (**8**), and **4** initiated by grinding in mortar (ae = 95%, Scheme 13) [43].



**Scheme 13.** Preparation of  $\beta$ -enaminones.

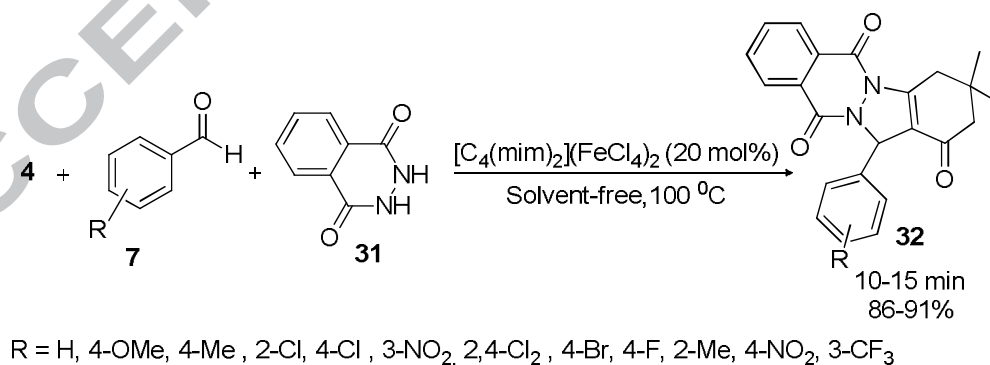
## 2.2. Reaction of dimedones under solvent-free conditions under heated medium

Chandrasekhar and co-workers [44] described an efficient one-pot, atom-economical, three-component reaction using  $\text{SiO}_2\text{-OK}$  (0.09 mol) as an efficient solid base reusable catalyst producing various substituted 2-amino-4*H*-benzo[*b*]pyrans (**9**) under solvent-free conditions at 80 °C within 1-8 min by 79-95% yield. Starch solution (4 ml) as a highly efficient homogenous catalyst at 50 °C has also achieved **9** within 25-75 min by 82-95% [45]. Heteroaromatic aldehydes such as thiophene-2-carbaldehyde and 2-furaldehyde have been used

the reaction lucratively. Tetrahydrobenzo[*b*]pyran derivatives are important class of heterocyclic compounds which used as anti-cancer, anticoagulant, diuretic, spasmolytic, and antianaphylactic agents [46].

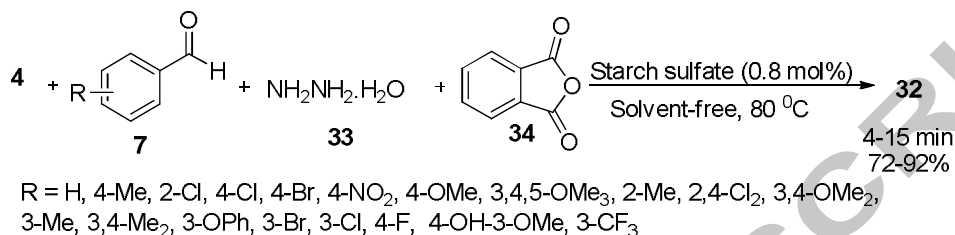
Mombani Godajdar and Soleimani in 2014, claimed that octahydroquinazolinones (**18**) has been performed via a three-component condensation promoting by magnetic dicationic liquid, 1,4-(butane-1,4-diyl)-bis-(3-methylimidazolium) di[tetrachloroferrate(III)]  $[(C_4(mim)_2)(FeCl_4)_2]$ , 20 mol%, at 100 °C in 50-120 min period by 79-91% [47]. Tangstophosphoric acid ( $H_3PW_{12}O_{40}$ , 2 mol%) at 80 °C within 1 h by 89% efficiency is another catalytic system to obtain 3,4-dihydropyrimidin-2(1*H*)-ones (**18**) via the reaction of benzaldehydes, dimedone, and urea at 2006 [48].

Mombani Godajda and co-workers [49] reported that 2*H*-indazolo[2,1-*b*]phthalazinetriones (**32**) has been achieved via the reaction of aldehydes (**7**), **4**, and phthalhydrazide (**31**) in the presence of  $[C_4(mim)_2](FeCl_4)_2$ , as a benign magnetic catalyst at 100 °C (ae = 91%, Scheme 14). The catalyst successfully separated by a strong magnetic field of 1.5 T. The recyclability of the mentioned magnetic room temperature dicationic ionic liquid (MRTDIL) has been examined within 5 run without activity loss. Phthalazine derivatives were reported to possess vasorelaxant activities.



**Scheme 14.** 2*H*-indazolo[2,1-*b*]phthalazinetriones.

Another practical and green procedure generated **32**, has been demonstrated through the four-component condensation of hydrazinium hydroxide (**33**), phthalic anhydride (**34**), **4**, and aromatic aldehydes (**7**) under thermal solvent-free conditions using starch sulphate as a solid acid catalyst (ae = 84%, Scheme 15) [50].



**Scheme 15.** 2*H*-indazolo[2,1-*b*]phthalazinetriones.

Hasaninejed et al. [51] also exhibited synthesis of **32** using sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO<sub>3</sub>H, 8 mol%) as an eco-friendly polymeric catalyst from the four-component condensation reaction under solvent-free conditions at 80 °C within 10-20 min by 80-93%. 1,4-Dimethyl(4-sulfobutyl)piperazinium hydrogen sulfate ([DMSBP][HSO<sub>4</sub>], 3 mol%), a bifunctional ionic liquid, has been reported by Habibi and Shamsian in 2014 to prepare **32** via a four-component condensation reaction of phthalic anhydride (**34**), hydrazinium hydroxide (**33**), **4**, and **7** under solvent-free conditions at 80 °C in 5-20 min period by 85-94% [52]. Sterically hindered aldehydes such as 1-naphthaldehyde has also carried out the reaction excellent.

The compound **32** has also obtained by Ziarani et al. [53] in 2014 by sulfonic acid functionalized SBA-15 (SBA-Pr-SO<sub>3</sub>H, 0.02 g) with a pore size of 6 nm at 80 °C within 5-15 min by 70-90%. Tungstosilicic acid (H<sub>4</sub>SiW<sub>12</sub>O<sub>40</sub>, 0.05 mmol) at 100 °C within 10-60 min by 60-95% [54], and nickel nanoparticle (Ni NPs, 10 mol%) at 80 °C within 10-14 min by 88-94% [55] are other reported systems to obtain **32**.

In 2011 Ghorbani-Vaghei et al. [56] explained that *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide (TBBDA, 0.05 g) and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) (PBBS, 0.1 g) at 80-100 °C under solvent-free conditions obtained **32**. The former did up the reaction within 10-60 min with 58-98% where the latter done it in a 25-150 min period with 40-87% efficiency. This is the only report that utilized aliphatic aldehydes to prepare the corresponding **32** adducts successfully. Reusable silica supported poly phosphoric acid (PPA-SiO<sub>2</sub>, 1g) at 100 °C during 6-24 min by 78-93% achieved **32** [57]. The authors claimed that the 1g of the prepared heterogeneous acid catalyst [58] contains 0.5 mmol of H<sup>+</sup>. phosphosulfonic acid (PSA, 7 mol%) is another novel environmentally benign heterogeneous solid acid catalyst to promote this three-component condensation under solvent-free conditions in 100 °C in 75-98% yields in 4-15 min [59].

Reusable silica supported preyssler heteropolyacid [H<sub>14</sub>[NaP<sub>5</sub>W<sub>30</sub>O<sub>110</sub>]/ SiO<sub>2</sub>, (50%)] (0.07 g) under solvent-free reflux conditions within 6-15 min by 80.5-94% is another efficient system reported by Gharib et al. [60] in 2013 to offer **32** derivatives. The solid product was purified by re-crystallization from aqueous ethanol (25%).

Wet cyanuric chloride (TCT, 0.03 g) at 100 °C by 89-97% during 10-25 min [61], *p*-TSA (0.3 mmol) in 80 °C within 10-20 min by 80-93% by Bazgir et al. [62], Ce(SO<sub>4</sub>)<sub>2</sub>·4H<sub>2</sub>O (2.5 mol%), as an eco-friendly catalyst, at 125 °C under solvent-free conditions within 5-10 min by 71-95% [63], 2-pyrrolidonium hydrogensulfate ([Hnhp][HSO<sub>4</sub>]), (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogensulfate, and triphenyl(propyl-3-sulphonyl)phosphonium toluenesulfonate, 5 mol% of each of the three acidic ionic liquids, at 80 °C within 4-16 min by 70-95% [64] are other systems to obtain **32** derivatives.

A series of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-ones (**26**) have been established by Hai-Feng et al. [65] utilizing *N*-(4-sulfonic acid)propyl triethylammonium hydrosulfate ([NSPTEA][HSO<sub>4</sub>], 40 mol%) at 120 °C within 1-20 min by 65-89%. The

researchers has also obtained the mentioned products in the presence of  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  (20 mol%) under the same conditions. In addition with different benzaldehydes, thiophene-2 carbaldehyde has also afforded the corresponding adduct. The compound **26** has also been achieved by Zare and Hasaninejad group in 2012 [66] in the presence of protic acidic ionic liquid pyrazinium di(hydrogen sulfate) ( $\text{Py}(\text{HSO}_4)_2$ , 10 mol%) at 100 °C within 15-45 min by 79-93% yield.

In 2012, a novel magnetic nanoparticle supported dual acidic ionic liquid catalyst (AIL@MNP) was synthesized by anchoring 3-sulfobutyl-1-(3-propyltriethoxysilane) imidazolium hydrogen sulfate onto the surface of silica-coated  $\text{Fe}_3\text{O}_4$  nanoparticles. This structure, due to the combination of nano-support features and flexible imidazolium linkers, acted as a “quasi-homogeneous” catalyst to prepare **26** at 90 °C within 35-65 min by 80-94% efficacy [67]. The catalyst could be easily recovered by an external magnet and reused six times without significant loss of catalytic activity. Trityl chloride ( $\text{TrCl}$ , 7 mol%) as a homogeneous organocatalyst, has also promoted the preparation of **26** at 110 °C within 40-70 min by 82-94% [68]. Khurana and Magoo has also claimed that **26** derivatives could be obtained by catalytic role of *p*-TSA (10 mol%) in  $[\text{bmim}]\text{BF}_4$  (0.5 ml) at solventless media at 80 °C within 2-3.5 h by 83-95% [69]. Trichloroacetic acid (0.1 g) at 120 °C has also promoted the preparation of **25** within short period of 10-30 min by 66-98% [70].

$\text{Cu}/\text{SiO}_2$  composites (0.05 g) under solvent-free conditions at 60 °C within 20-35 min by 80-92% yield has been accounted as a reusable catalyst by Oskooie and co-workers in 2011 is a straightforward procedure for the synthesis of **26** [71]. Zinc oxide nanoparticles ( $\text{ZnO}$  NPs, 10 mol%) at 120 °C within 10-30 min by 85-95% by Safaei-Ghomi et al. [72], and *p*-TSA (2 mol%) under neat conditions at 100 °C utilizing microwaves (300 W) within 2.5-3.5 min with 84-91% [73] by Khurana group have been reported as efficient catalytic systems to prepare **26** adducts. Khurana research group have also examined the reaction in

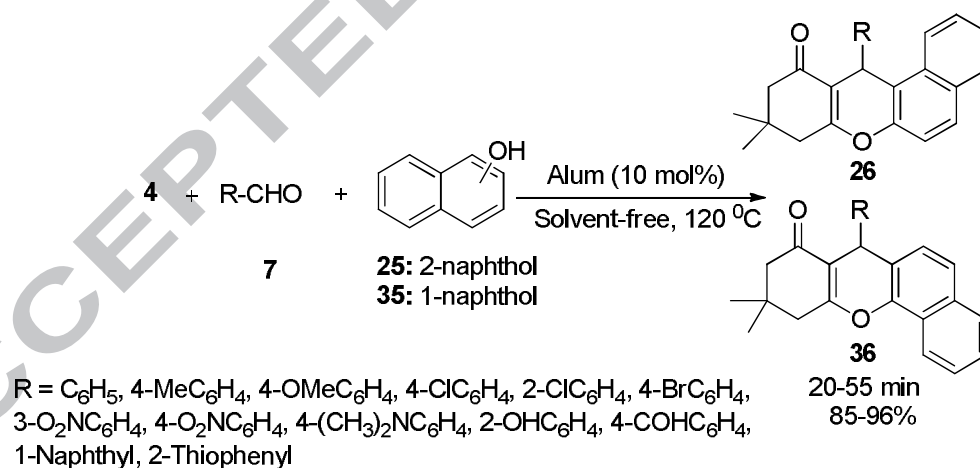


refluxing water in the presence of 2 mol% of *p*-TSA within 2.5-3.5 h by 85-91%. The results confirmed that solvent-free situation achieved better data.

Rice husk (RiK, 0.5 g), as a green and cheap reagent, have also utilized for the promotion of the synthesis of 12-aryl-8,9,10,12-tetrahydrobenzo[*a*]xanthen-11-one derivatives (**26**, ATXOs) via three-component reaction of aldehydes (**7**),  $\beta$ -naphthol (**25**), and **4** under solvent-free conditions at 90 °C within 30-75 min by 93-98% [74].

Other promoters to obtain **26** derivatives included citric acid (20 mol%) under solvent-free condition at 120 °C within 20-25 min by 88-92% [75], and  $\text{H}_4\text{SiW}_{12}\text{O}_{40}$  (SiWA, 3.5 mol%) at 100 °C within 15-40 min by 82-91% [76].

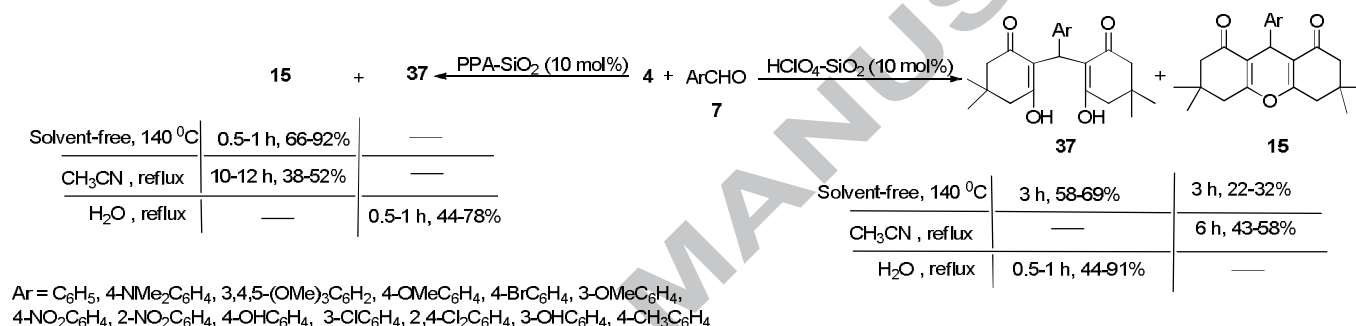
Kapoor group in 2014 reported alum as an efficient and benign oxide to obtain **26** via the one-pot, three-component condensation of aldehydes (**7**),  $\beta$ -naphthol (**25**), and **4**. They have also exchanged **25** to  $\alpha$ -naphthol (**35**) to afford various 12-substituted-8,9,10,12-tetrahydrobenzoxanthen-11-ones (**36**) in excellent yields under solvent-free conditions at 120 °C (ae = 91%, Scheme 16) [77].



**Scheme 16.** Various 12-substituted-8,9,10,12-tetrahydrobenzoxanthen-11-ones.

Kantevari et al. [78] reported that the reaction of dimesone (**4**) with various aldehydes (**7**) at 140 °C using PPA–SiO<sub>2</sub> gave 1,8-dioxo-octahydroxanthenes (**15**); whereas in the

presence of  $\text{HClO}_4\text{-SiO}_2$  as catalyst give **15** in addition with 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**37**) as by-product. Carrying out the reaction in refluxing water utilizing both of the catalysts achieved only **15**. Surprisingly changing the solvent to acetonitrile in refluxing mode, gave incredible results. In the case of  $\text{HClO}_4\text{-SiO}_2$  only **37** obtained and utilizing  $\text{PPA-SiO}_2$  gave **15** as the sole product in very good yields (Scheme 17). The author's hypothesis supported the fact that reaction proceeded via one-pot Knoevenagel condensation, Michael addition, and cyclodehydration respectively.



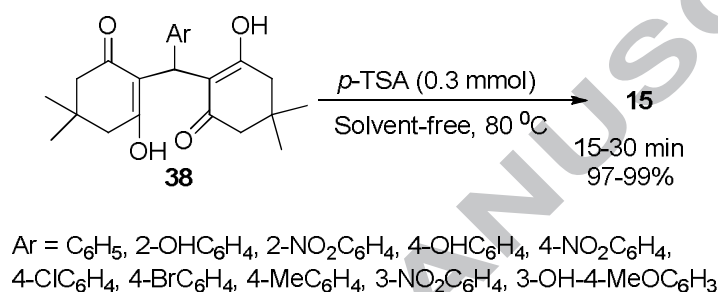
**Scheme 17.** 1,8-Dioxo-octahydroxanthenes and 1,8-dioxo-octahydroxanthenes.

Wu et al. [79] described synthesis of **15** under solvent-free conditions at 110 °C in the presence of silica chloride ( $\text{SiO}_2\text{-Cl}$ , 250 mg) within 3-4 h by 86-91%. In addition,  $[\text{C}_4(\text{mim})_2](\text{FeCl}_4)_2$ , the magnetic room temperature dicationic ionic liquid (MRTDIL), which has been prepared via the reaction of 1,4-dichlorobutane and 1-methylimidazole, is another recyclable catalyst for the synthesis of **15** at 80 °C within 10-15 min by 87-92% [80].

The synthesized ZnO nanoparticles (10 mol%) via Shen group method [81] through the reaction of zinc acetate and oxalic acid, has also been catalysed the preparation of **15** under solvent-free conditions at 80 °C within 15-25 min by 82-97% [82]. Ferric hydrogen sulfate (0.05 g) at 120 °C within 5-18 min by 81-97% yield [83], hydroxylamine-o-sulfonic Acid (HOSA, 5 mol%), as a task specific catalyst, at 90 °C within 15-40 min by 80-95%

yield [84], and  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  (2 mol%) at 85 °C within 10-35 min by 90-97% [85] are other catalytic systems to prepare **15** derivatives. In addition Zhang and co-workers in 2008 has also utilized  $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$  (10 mol%) at 120 °C within 40-80 min by 75-96% to obtain **15** [86].

Bayat and co-workers in 2009 utilized *p*-TSA (0.3 mmol) under solvent-free conditions at 80 °C to obtain **15** from cyclization of 2,2-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**38**) within 15-30 min (ae = 95%, Scheme 18) [87].



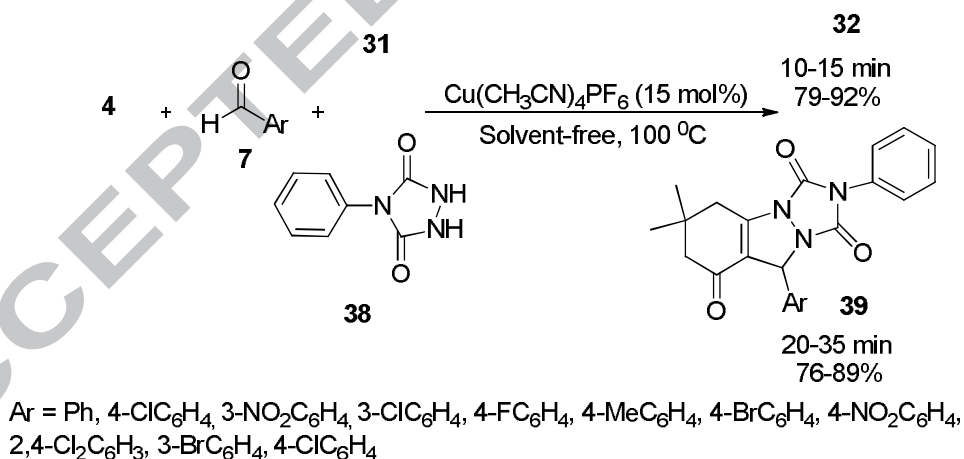
**Scheme 18.** Preparing **15** from cyclization of 2,2-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one).

Another efficient protocol to achieve **15** has been developed in the presence of  $\text{InCl}_3$  (15 mol%) or  $\text{P}_2\text{O}_5$  (20 mol%) under solvent-free conditions at 100 °C [88]. The former catalyst was effectual in 15-70 min long by 58-98%, while the latter done the transformation within 20-74 min by 56-96%. In addition with various benzaldehyde derivatives, heteroaromatic analogous such as thione-2-carbaldehyde and phenylethanal has also afforded the mentioned adducts successfully. Some products showed optical properties as new luminescence materials or fluorescence probes

Zare and co-workers [89] reported triethylamine-bonded sulfonic acid ( $[\text{Et}_3\text{N}-\text{SO}_3\text{H}]\text{Cl}$ , 25 mol%) a versatile system for preparation of **15** under solvent-free conditions at moderate temperature, 80 °C, within 30-60 min by 85-97%. Cinnamaldehyde has also get the corresponding **15** product without any by-product formation.

Some more catalytic systems to prepare **15** are: montmorillonite K10 (0.3 g) at 100 °C within 1-2 h by 75-90% yield by Bazgir et al. in 2008 [90], saccharin sulfonic acid (SaSA, 15 mol%) at 90 °C within 10-45 min by 90-97% yield [91], nano silica-supported ferric chloride ( $\text{FeCl}_3\text{-SiO}_2$  np, 20 mol%), a brownish synthesized powder, at 100 °C within 15-35 min by 80-95% examined by Safaei-Ghomi et al. [92], and phosphosulfonic acid (5 mol%) at 110 °C within 30-55 min by 65-98% [93]. All the four catalysts are reusable within several cycles without activity deficiency.

Tetrakis(acetonitrile)copper(I) hexafluorophosphate,  $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ , was explored as an efficient catalyst to promote the three-component reaction of aryl aldehydes (**7**), dimedone (**4**), and urazole (**38**) or phthalhydrazide (**31**) to afford the corresponding triazolo[1,2-*a*]indazole-1,3,8-trione (**39**) and 2*H*-indazolo[2,1-*b*]phthalazine-trione (**32**) derivatives respectively in high yields. The reactions were conducted at 100 °C under solvent-free conditions (Scheme 19) [94]. The atom economy to preparation of both **32** and **39** is 91%.

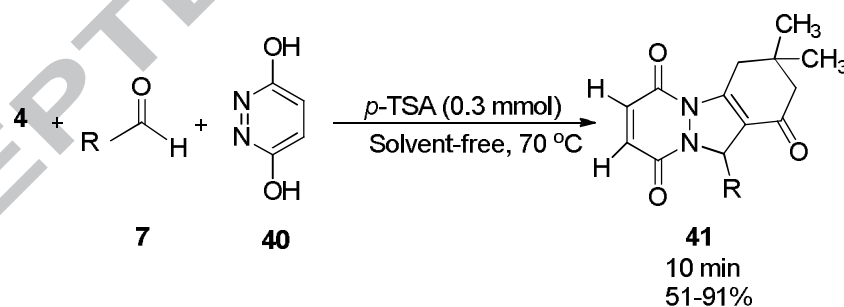


**Scheme 19.** Triazolo[1,2-*a*]indazole-1,3,8-triones and 2*H*-indazolo[2,1-*b*]phthalazine-triones.

The **39** derivatives have also been obtained based on the three-component condensation at 80 °C using *p*-TSA (0.3 mmol) by Bazgir et al. within 15-30 min by 78-90%

[95]. In addition, nanosilica sulfuric acid (nano  $\text{SiO}_2\text{-OSO}_3\text{H}$ , 125 mg), in which nano silica has been extracted from rice husk, through method A: conventional heating at 80 °C, and method B: microwave irradiation (400 W) [96] also prepared **39**. The results in method A obtained within 20-35 min by 80-90% and in method B in 10 min by 92-96%. Sulfonated polyethylene glycol ( $\text{PEG-SO}_3\text{H}$ , 10 mol%) at 80 °C in 30-360 min by 82-92% by Hasaninejad et al. is another procedure trepanned to **39** [97]. Spirotryprostatins, natural alkaloids isolated from the fermentation broth of *Aspergillus fumigatus*, are indolines, including **39**-like structure, that been identified as novel inhibitor of microtubule assembly [98].

An efficient synthesis of biologically interesting pyridazinoindazolone derivatives (**41**) was achieved via a one-pot three-component *p*-TSA-catalysed reaction of dimedone (**4**), differently substituted (hetero)aromatic and aliphatic aldehydes (**7**), and 3,6-dihydropyridazine (**40**) under solvent-free conditions at 70 °C with the ae = 82% (Scheme 20) [99]. Heterocycles containing bridgehead hydrazine such as diftalone, has been used as a NSAID [100].

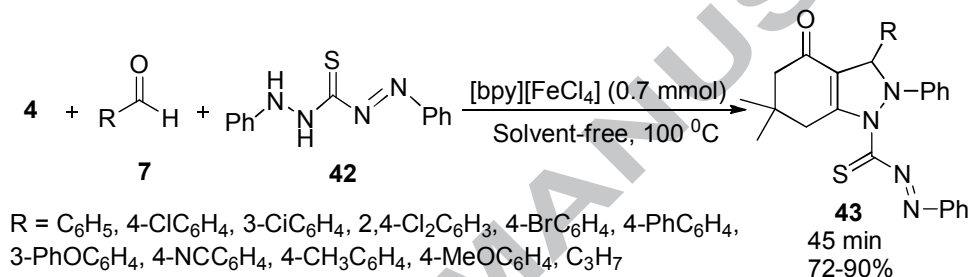


R =  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $\text{C}_6\text{H}_5$ , 4-Cl- $\text{C}_6\text{H}_4$ , 4- $\text{O}_2\text{N-C}_6\text{H}_4$ , (*E*)-1-Nitro-2-(prop-1-en-1-yl)benzene, 3,6-Dimethyl-4*H*-chromen-4-one

**Scheme 20.** Pyridazinoindazolone derivatives.

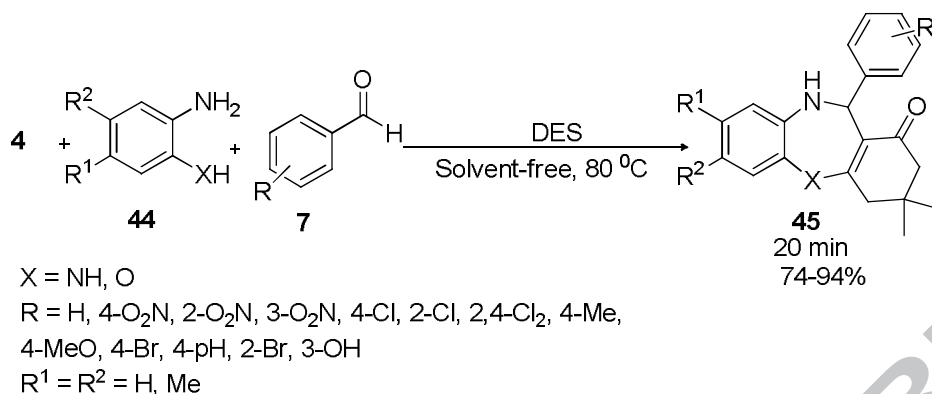
Synthesis of **41** has also been reported by Bazgir et al. [101] in 2008 using mentioned substrates under solvent-free conditions at 80 °C using *p*-TSA (0.1 g) within 20-40 min by 46-55%. They only used benzaldehyde analogous.

A novel and one-pot procedure for the synthesis of *N*-(phenylimino)indazole-1-carbothioamides (**43**) was reported via three-component condensation of aldehydes (**7**), dithizone (**42**), and **4** in the presence of Lewis acid ionic liquid [bpy][FeCl<sub>4</sub>] under solvent-free conditions at 100 °C (Scheme 21) [102]. Indazole-containing heterocyclic compounds, contained different medicinal properties such as anti-tuberculosis effects [103].



**Scheme 21.** *N*-(phenylimino)indazole-1-carbothioamides.

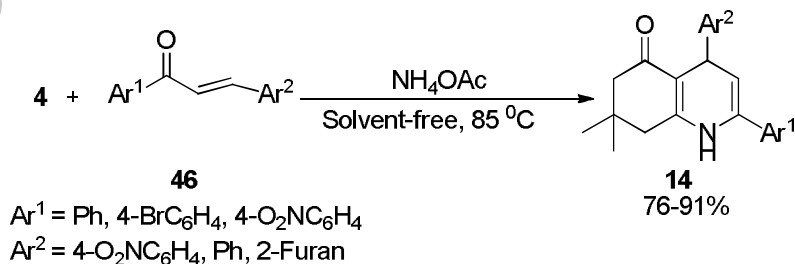
In 2016 Shabani et al. reported combination of choline chloride and urea (1:2) as a deep eutectic solvent to prepare benzo-fused seven-membered heterocycles, including tricyclic 1,4-benzodiazepines and 1,4-benzoxazepines (**45**), with the atom economy 90%, via a one-pot, three-component reaction of *o*-phenylenediamine/ 2-aminophenol (**44**), dimedone (**4**), and various aromatic aldehydes at 80 °C (Scheme 22) [104].



**Scheme 22.** Tricyclic 1,4-benzodiazepines and 1,4-benzoxazepines.

A powerful and environmentally benign method has been demonstrated in 2015 by Naeimi and Foroughi for the one-pot synthesis of 4-substituted-1,5-benzodiazepines (**45**) via the three-component reaction of a series of **7** with **4**, and *o*-phenylenediamine (**44**) using *N*-methyl-2-pyrrolidonium hydrogen sulphate ([H-NMP][HSO<sub>4</sub>]), as a Brönsted acidic ionic liquid catalyst, under solvent-free conditions at 100 °C within 13-19 min by 71-85% [105]. 1,5-Dibenzodiazepines exhibit inhibitory activities towards hepatitis C virus (HCV) NS5B [106].

Chen and co-workers [107] reported preparation a series of polyhydroquinolines (**14**) through the reaction of chalcones (**46**) with dimedone **4** in the presence of ammonium formate under solvent-free conditions at 85 °C (Scheme 23).

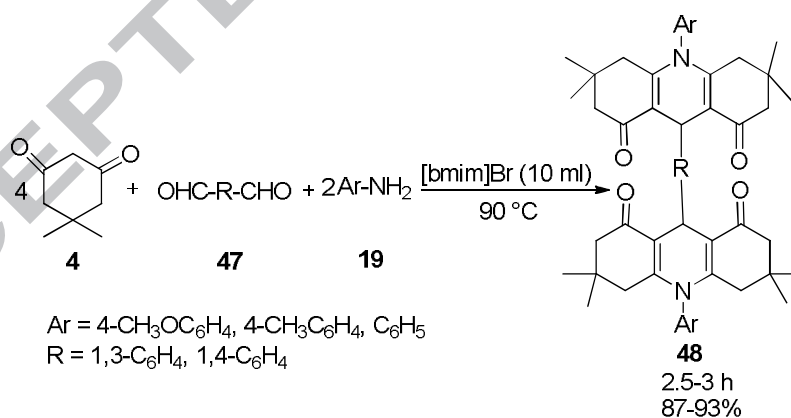


**Scheme 23.** Polyhydroquinolines.

A simple protocol has been developed for the one-pot multi-component synthesis of 1,8-dioxo-octahydroxanthenes (**15**) from the reaction of aromatic aldehydes (**7**), dimedone **4**, and also *N*-aryl-1,8-dioxodecahydroacridines (**20**) in excellent yields using ammonium chloride (20 mol%), as a low-cost and nontoxic eco-friendly catalyst, under solvent-free conditions at 120 °C [108]. Under the mentioned conditions the corresponding products obtained within 0.75-2 h by 84-97% yield.

Tetrabutylammonium hexatungstate ([TBA]<sub>2</sub>[W<sub>6</sub>O<sub>19</sub>]) has been utilized to promote the one-pot three-component synthesis of 1,8-dioxodecahydroacridines (**20/ 21**) under neat conditions at 120 °C described by Davoodnia et al. in 2012 within 7-14 min by 84-94% yield [109]. In addition with aromatic aldehydes ethanal and propanal has also derived the products successfully.

1-Butyl-3-methylimidazolium bromide ([bmim]Br, 10 ml) under neat conditions at 120 °C within 15 min to 4.5 h by 60-99% yield is another procedure to prepare **20/ 21** by Shen et al. [110]. Under the same conditions they also prepared a series of bis(decahydroacridine-1,8-dione) (**48**) with the atom economy of 90% (Scheme 24).



**Scheme 24.** Bis(decahydroacridine-1,8-dione).

Moeinpour et al. in 2012 described silica gel-supported polyphosphoric acid (PPA-SiO<sub>2</sub>, 0.02 g), as a reusable catalyst, for the synthesis of **20/ 21** via one-pot three-component



condensation under solvent-free conditions at 100 °C within 5-25 min by 88-95% [111]. Although in 2016 Khazaei and co-workers reported that nano TiO<sub>2</sub> (10 mol%) is another synthetic nanoparticle which accelerated preparation of **20/ 21** in the solventless 75 °C media within 10-60 min by 70-90% yield [112]. There are some other catalytic systems yielded **20/ 21** derivatives which including: carbon-based solid acid catalyst (CBSA, 0.03 g) [113], as a highly efficient, eco-friendly and recyclable heterogeneous catalyst utilized at 100 °C by Hara et al. within 15-50 min by 80-93% [114], sulfonic acid functionalized silica (SiO<sub>2</sub>-Pr-SO<sub>3</sub>H, 0.02 g) at 120 °C within 2 h by 82-95% [115], sulfonic acid functionalized nanoporous silica (SBA-Pr-SO<sub>3</sub>H, 0.02 g) within 25-45 min by 58-92% [116] both by Ziarani et al., and alumina supported polyphosphoric acid (PPA/Al<sub>2</sub>O<sub>3</sub>, 0.02 g) at 120 °C within 5-30 min by 83-93% by Davoodnia et al. [112] in 2014.

A three-component Hantzsch-type condensation of anilines (**19**), **4**, and benzaldehyde led to the formation of 3,4,6,7,9,10-hexahydro-3,3,6,6-tetramethyl-9-phenylacridine-1,8(2*H*,5*H*)-diones (**20**) under solvent-free conditions with microwaves with the power of 400 W, 105 °C, and 18.3 bar Within 8-30 min by 63-85% [117].

Preparation of **20** have also examined in the presence of Fe<sub>3</sub>O<sub>4</sub> nanoparticles (10 mol%) at 120 °C within 12-50 min by 70-95% [118]. 4-Arylacridinedione derivatives (**21**) has been performed at 80 °C, using Zr(HPO<sub>4</sub>)<sub>2</sub>.H<sub>2</sub>O ( $\alpha$ -ZrP, 10 mol%) within 2 h by 93-96% [119].

In 2014 a multi-component Hantzsch synthesis of acridinediones (**20**) in the presence of salicylic acid (20 mol%) as an efficient catalyst, under solvent-free conditions at 80 °C in 67-90% yield and 3-5 h time is reported [120].

A bio-supported, biodegradable and renewable solid acid catalyst (cellulose-SO<sub>3</sub>H, 0.07 g) was used for the three-component reactions of **4**, malononitrile (**8**), and isatin (**29**) to

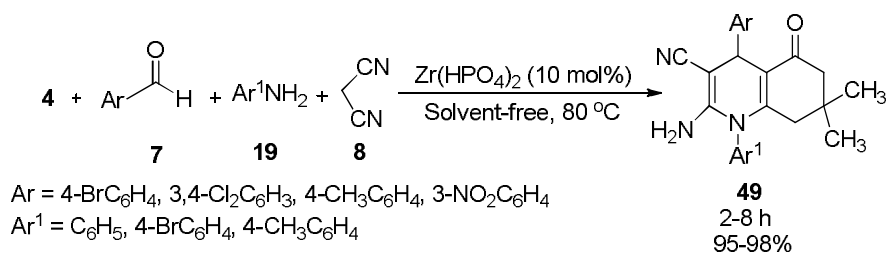
synthesize spirooxindole (**30**) under solvent-free conditions at 55 °C within 30 min by 65% yield [121].

The electrosynthesis of **30** has also been reported in an undivided cell in the presence of sodium bromide as an electrolyte at 50 °C and propanol, as solvent, under constant current density 10 mA/cm<sup>2</sup>. This electrocatalytic transformation has been done via the electro-generated base of the anion of propanol [122].

Compounds **12** has been reported by Shiri et al. through the four-component condensation in the presence of 1,3-disulfonic acid imidazolium hydrogen sulfate as (DSIMHS, 0.25 mmol), as an efficient and recyclable ionic liquid, under solvent-free conditions at 70 °C. The products obtained within 3-15 min by 88-94% yield [123]. They have also obtained in the catalytic role of SBA-Pr-SO<sub>3</sub>H (0.05 g) via the Hantzsch four-component condensation reaction of aldehydes (**7**),  $\beta$ -ketoester (**10**), **4**, and **11** under solvent-free conditions at 80 °C within 10-18 min by 75-90% [124]. Cinnamaldehyde has also gave the corresponding adduct successfully.

Carbon-based solid acid (CBSA, 0.02 g) at 80 °C within 18-35 min by 87-95% is another reported promotor to obtain **12** demonstrated by Davoodnia and Khojastehnezhad in 2012 [125].

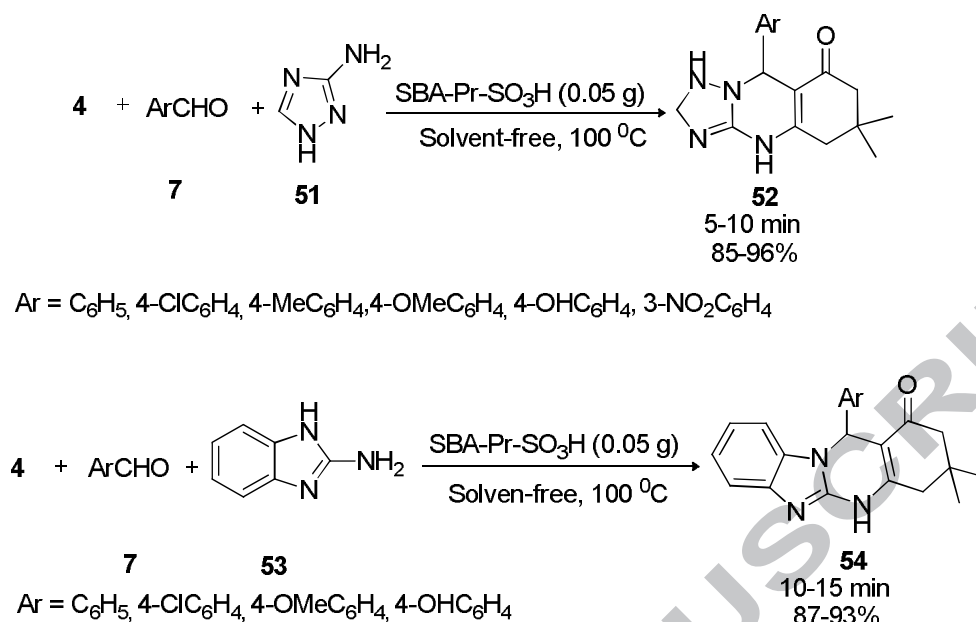
In 2013 2-amino-7,7-dimethyl-5-oxo-1,4-diaryl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitriles (**49**) were synthesized by Abdolmohammadi group through the one-pot four-component reaction of aromatic aldehydes (**7**), malononitrile (**8**), dimedone (**4**), and arylamines (**19**) in the presence of Zr(HPO<sub>4</sub>)<sub>2</sub>.H<sub>2</sub>O ( $\alpha$ -ZrP) as an effective and recyclable solid acid catalyst under solvent-free conditions at 80 °C with the ae of 85% (Scheme 25) [126]. Several disubstituted polyhydroquinolines exhibited promising in vivo antihyperglycemic activity [127].



**Scheme 25.** 2-Amino-7,7-dimethyl-5-oxo-1,4-diaryl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile.

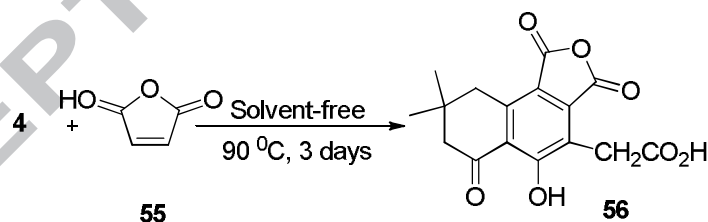
In 2014 the one-pot synthesis of benzo[*c*]acridines (**27**) via the three-component condensation reaction of aromatic aldehydes (**7**), 1-naphthylamine (**50**), and **4** using SBA-Pr-SO<sub>3</sub>H (0.02 g) under solvent-free conditions at 140 °C within 2-13 min by 83-96% yield [128].

Ziarani research group [129] in 2011 reported SBA-Pr-SO<sub>3</sub>H with a pore size of 6 nm as an efficient heterogeneous nanoporous solid acid catalyst in the green one-pot synthesis of triazoloquinazolinones (**52**) and benzimidazoquinazolinones (**54**) from the reaction of aromatic aldehydes (**7**) with 3-amino-1,2,4-triazole (**51**)/ 2-aminobenzimidazole (**53**), and dimedone (**4**) under solvent-free conditions at 100 °C (Scheme 26). The atom economy of the procedure is 90%. Quinazolinone derivatives showed many biological activities such antidepressant [130].



**Scheme 26.** Triazoloquinazolinones and benzimidazoquinazolinones.

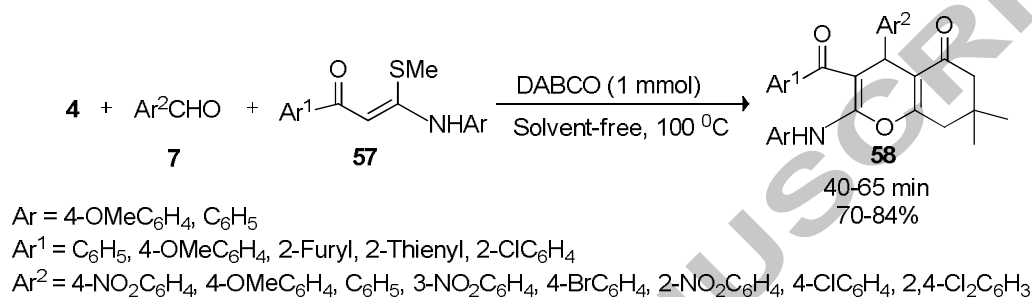
In 1968 Molton [125] described catalyst-free condensation of maleic anhydride (**55**) with **4** to achieve 3-carboxymethyl-5,6,7,8-tetrahydro-4-hydroxy-7,7-dimethyl-5-oxonaphthalene-1,2-dicarboxylic anhydride (**56**) under solvent-free conditions at 90 °C (Scheme 27).



**Scheme 27.** 3-Carboxymethyl-5,6,7,8-tetrahydro-4-hydroxy-7,7-dimethyl-5-oxonaphthalene-1,2-dicarboxylic anhydride.

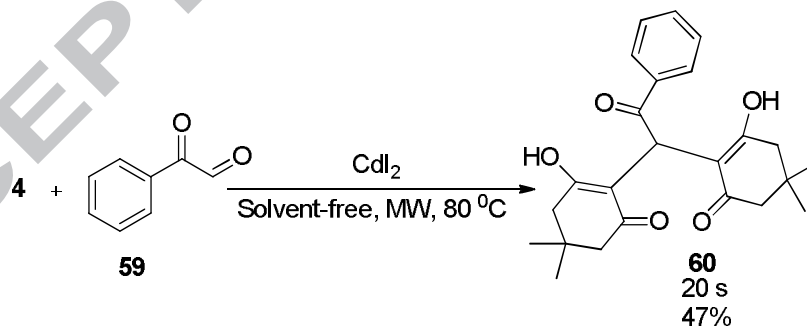
An efficient and convergent route to 3-aryl-4-aryl-2-arylamino-4,6,7,8-tetrahydrochromen-5-ones (**58**) has been developed by an one-pot three-component domino coupling of  $\alpha$ -oxoketene-*N,S*-arylaminoacetals (**57**), aromatic aldehydes (**7**), and **4** in the

presence of DABCO under solvent-free conditions at 100 °C in high yields (Scheme 28) [131]. The merit of this cascade Knoevenagel condensation/ Michael addition/ cyclization sequence is highlighted by its high atom economy (87%), good yields, efficiency of producing three new bonds (two C–C and one C–O), and one stereocenter in a single operation.



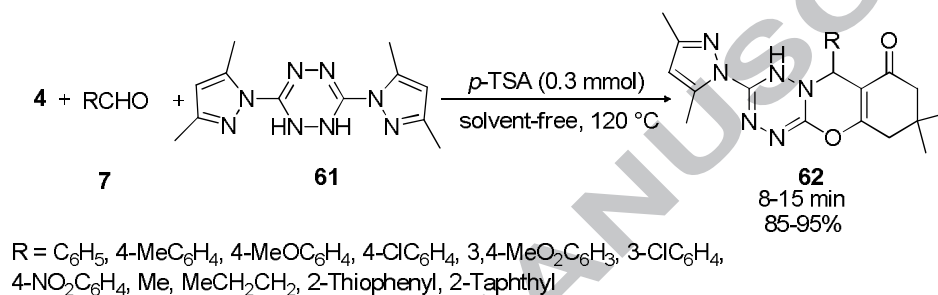
**Scheme 28.** 3-Aroyl-4-aryl-2-arylamino-4,6,7,8-tetrahydrochromen-5-ones.

2,2'-(2-oxo-2-phenyl-1,1-ethanediyl)bis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**60**) obtained by the reaction of **4** and arylglyoxal (**59**), using catalytic amounts of CdI<sub>2</sub> under solvent-free conditions and microwave irradiation in 80 °C within 20 s by 47% yield and 95% atom economy (Scheme 29) [132, 133].



**Scheme 29.** 2,2'-(2-Oxo-2-phenyl-1,1-ethanediyl)bis(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one).

Adib et al. [134] in 2015 reported a one-pot, three-component synthesis of 3-(1*H*-pyrazol-1-yl)-4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones (**62**) which involves heating a mixture of 1,2-dihydro-3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (**61**), aldehydes (**7**), and **4** in the presence of a catalytic The adduct which are bridgehead-fused 6:6:6 systems with one ring-junction nitrogen atom has been get via the cyclocondensation of aliphatic aldehydes in addition with aromatic aldehydes. The atom economy is 76%.



**Scheme 30.** 3-(1*H*-pyrazol-1-yl)-4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones.

### 3. Reaction of dimedone in aqueous media

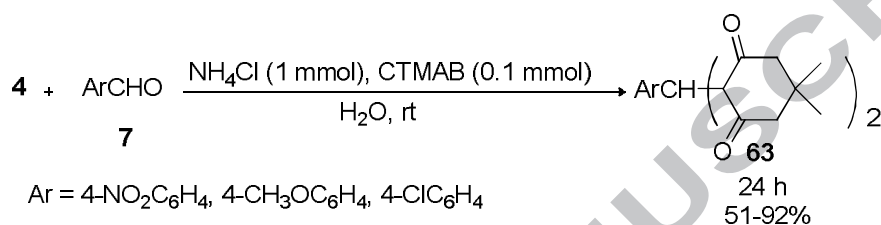
Water has emerged as a versatile solvent for organic chemistry in recent years. Water as a solvent is not only inexpensive and environmentally benign, but also gives completely new reactivity. In many cases, due to hydrophobic effects, using water as a solvent not only accelerated reaction rates but also enhanced reaction selectivity, even when the reactants are sparingly soluble or insoluble in this medium [135].

#### 3.1. Reaction in dimedone at room temperature aqueous media

A simple and efficient one-pot procedure for the synthesis of **15** in water under ultrasound irradiation (frequency of 20 KHz) at room temperature has been demonstrated by condensation of dimedone (**4**) with various aromatic aldehydes (**7**) in the presence of

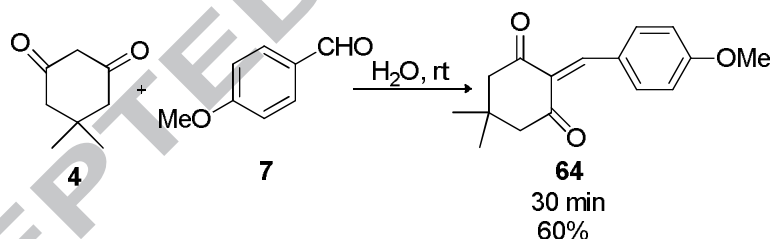
Brønsted acidic ionic liquid ( $[H-NMP]^+[HSO_4]^-$ , 20 mol%) [136] within 40-75 min by 70-94% [137].

Ren et al. [138] in 2002 reported a new route of Knoevenagel condensation of aromatic aldehydes (**7**) with 2 equivalent of **4** in the presence of cetyltrimethyl ammonium bromide (CTMAB) and ammonium chloride at room temperature in water to obtain 1,8-xanthenediones with ae = 95% (**63**) (Scheme 31).



**Scheme 31.** 1,8-Xanthenediones.

Knoevenagel condensation of 4-methoxybenzaldehyde and **4** has been performed for synthesis of **66** adduct in water at room temperature with ae = 93% (Scheme 32) [139].



**Scheme 32.** Knoevenagel condensation of 4-methoxybenzaldehyde and **4**.

Bayat and co-workers in 2009 reported a simple unanalyzed method for the synthesis of Compound **37** under solvent-free aqueous conditions at room temperature within 20-60 min by 96-99% [140].  $\text{ZnCl}_2$  (0.125 mmol) is another catalyst to obtain **37** in water at room temperature within 15-60 min by 83-97% [141]. Other catalytic systems in room temperature aqueous medium to afford **37** includes: *L*-lysine (20 mol%) within 5-9 h by 88-95% in 2010

by Shang et al. [142], and sulfonic acid-functionalized silica-coated nano-Fe<sub>3</sub>O<sub>4</sub> particles (Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-SO<sub>3</sub>H, 0.01 g) in 60-170 min period by 44-97% [143].

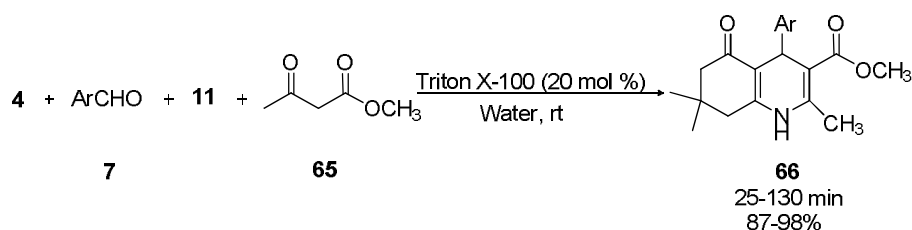
Biologically important pyran derivatives **9** has been prepared by Pal and Saha [144] in 2013 via a three-component condensation of dimedone (**4**), aromatic aldehydes (**7**), and malononitrile (**8**) by fermented baker's yeast (200 mg) within 40-60 min by 81-92%. Mossadegh and Hasankhani in 2014 [145] has also reported [*N,N'*-bis(benzoylacetone)-1,2-ethylenediimine]Mn(III) chloride [146] ((bzacen)MnCl, 2.5 mol%) within 45-60 min by 81-92% to get **9** derivatives. Sadek et al. [147] in 2010 also reported this three-component reaction to obtain **9** in the presence of pipyridine (2 drops) in water with 30-60 min by 91-95%. These compounds has also obtained in the presence of Zn(Phen)<sub>2</sub>Cl<sub>2</sub> (2 mol%) in water at room temperature within 5 min by 90-100% [148].

Diethylene glycol-bis(3-methylimidazolium) dihydroxide ([DiEG(mim)<sub>2</sub>][OH]<sub>2</sub>, 10 mol%), as a dicationic ionic liquid, has been reported by Niknam et al. to prepare **9** in water at room temperature within 15-45 min by 85-92% yield [149].

A protic pyridinium ionic liquid, 2-methylpyridinium trifluoromethanesulfonate ([2-MPyH]OTf, 1 mol%), catalyzed the four-component Hantzsch condensation reaction of **4**, ethyl acetoacetate (**10**), ammonium acetate (**11**), and various aromatic and aliphatic aldehydes (**7**) in water at room temperature affords polyhydroquinoline derivatives (**12**) within 1-15 min in 92-98% yields by Nourozi et al. in 2013 successfully [150].

A facile and efficient synthesis of hexahydroquinoline derivatives (**66**) was developed via a four-component condensation reaction of aldehydes (**7**), **4**, methyl acetoacetate (**65**) and ammonium acetate (**11**) in the presence of the non-ionic surfactant Triton X-100 in water at room temperature was reported by Poor Heravi et al. with ae = 75% (Scheme 33) [151].

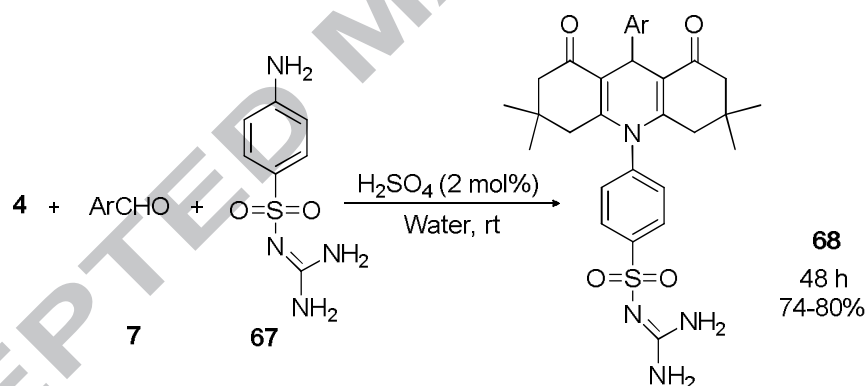




Ar = C<sub>6</sub>H<sub>5</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 2-BrC<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 2-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 2-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 2-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 2-FC<sub>6</sub>H<sub>4</sub>, 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-C<sub>6</sub>H<sub>5</sub>C<sub>6</sub>H<sub>4</sub>, 1-Naphthyl, 2-NFuryl

**Scheme 33.** Hexahydroquinoline derivatives.

Reaction of **4**, 4-amino-*N*-(diaminomethylene)benzenesulfonamide (**67**), and aromatic aldehydes (**7**) was realized using sulfuric acid (2 mol%) as a cheap catalyst for the synthesis of novel acridine sulfonamide compounds (**68**) providing high yields in water as the solvent at room temperature (ae = 91%, Scheme 34) [152]. The adducts showed inhibitory properties against human carbonic anhydrase isozymes (hCA I and hCA II).

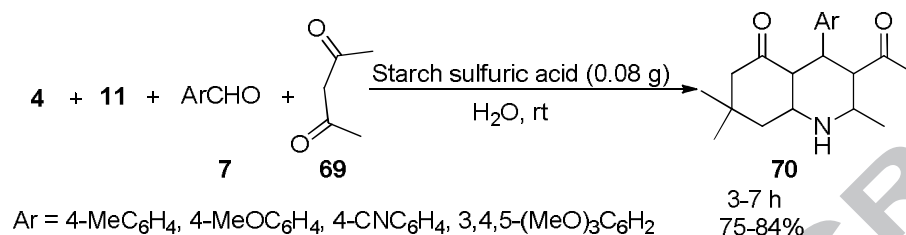


Ar = 4-CNC<sub>6</sub>H<sub>4</sub>, 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 2,4-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 5-Br-2-OHC<sub>6</sub>H<sub>3</sub>, 4-OHC<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-C<sub>2</sub>H<sub>5</sub>C<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>SC<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 2,4-(CH<sub>3</sub>O)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 3,4-(CH<sub>3</sub>O)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

**Scheme 34.** Novel acridine sulfonamide compounds.

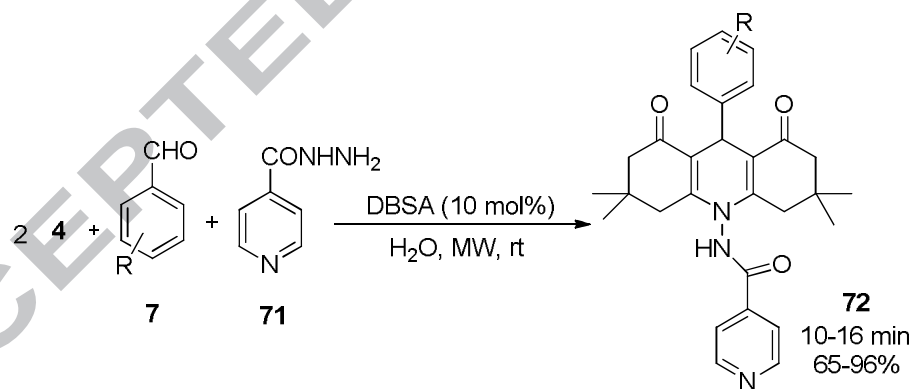
In 2013 the one-pot three-component reaction catalyzed by bis(*N*-2-bromophenyl-salicydenaminato)copper(II) complex, Cu(II) Schiff-base complex (1 mol%) [153], in water got the corresponding 1,8-dioxodecahydroacridines (20/ 21) with 93-98% yields in 5-20 min period [154].

Starch sulfuric acid was utilized as efficient catalyst of some novel polyhydroquinoline derivatives (**70**) via the Hantzsch reaction of various aromatic aldehydes (**7**), **4**, **11**, and acetyl acetone (**69**) in aqua (ae = 74%, Scheme 35) [155].



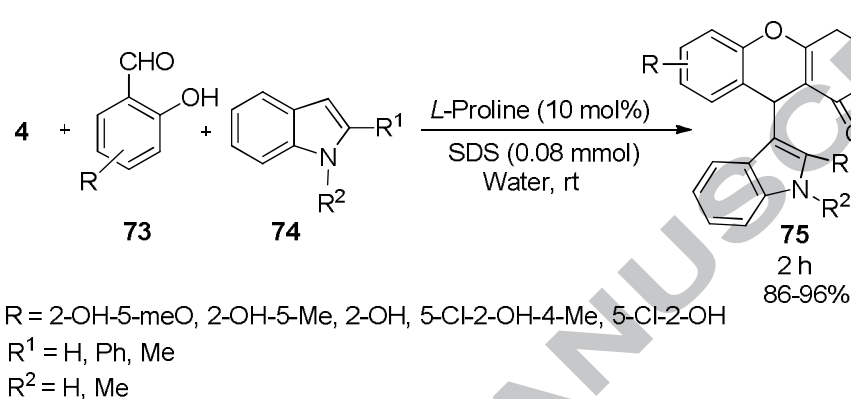
**Scheme 35.** Novel polyhydroquinolines.

A series of novel isoniazid (INH) analogues (**72**) were synthesized by microwave-assisted one-pot reaction of isoniazid (INH) (**71**), various benzaldehydes (**7**), and **4** in water with catalytic amount of *p*-dodecylbenzenesulfonic acid (DBSA) [156] in water at room temperature (ae = 90%, Scheme 36) [157]. INHs is antitubercular agent which is not effective against MDR-TB.



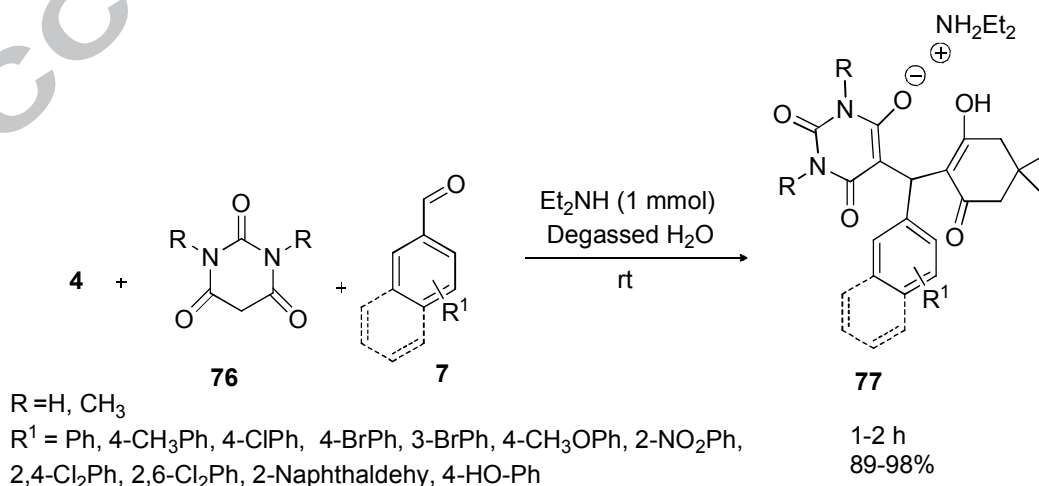
**Scheme 36.** Novel isoniazid (INH) analogues.

An operational and facile *L*-proline-catalyzed three-component coupling of **4**, 2-hydroxybenzaldehydes (**73**), and indoles (**74**) in the presence of an anionic surfactant, sodium dodecyl sulfate (SDS), above its critical micellar concentration (cmc) [2 ml water, 0.08 mmol SDS, 5 cmc], has been accomplished by Ganguly group in 2012 in water at room temperature to get 9-(1*H*-indol-3-yl)-xanthen-4-(9*H*)-ones (**75**) (ae = 96%, Scheme 37) [158].



**Scheme 37.** 9-(1*H*-indol-3-yl)-xanthen-4-(9*H*)-ones.

Barakat and co-workers [159, 160] in 2014 described a convenient one-pot method for the efficient synthesis of the novel zwitterion derivatives (**77**) via a three-component condensation reaction of barbituric acid derivatives (**76**), **4**, and various aldehydes (**7**) in the presence of diethylamine in degassed aqueous media at room temperature (ae = 89%, Scheme 38).



**Scheme 38.** Synthesis of the novel zwitterion derivatives**3.2. Reaction in dimedone in heated aqueous media**

A series of 10-methyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione derivatives (**21**/ **48**) were synthesized by one-pot reaction of aromatic aldehydes (**7**)/ benzaldehyde (**47**), **4**, and methylamine (**19**) in refluxing water under microwave irradiation (200 W) in the presence of 3 mmol NaOAc within 2-10 min by 58-96% [161]. In 2009 Balalaie and co-workers reported synthesis of **20** which developed in the presence of ammonium chloride, or  $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$  or *L*-proline separately in refluxing water within 2-3 h by 82-97%. The results confirmed that the catalytic activity of three utilized catalyst based on the catalyst amount is in this manner: *L*-proline > ammonium chloride >  $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$  [162]. Compounds **20** has also prepared via a catalyst-free procedure reported by Singh group in 2011 under microwave irradiation (220 W) in 100 °C in aqueous media within 3-5 min by 88-95% [163]. They have also generated in refluxing water in the presence of preyssler heteropolyacid catalyst ( $\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$ , 0.01 g) within 130-190 min by 80-94% by Gharib and co-workers in 2012 [164].

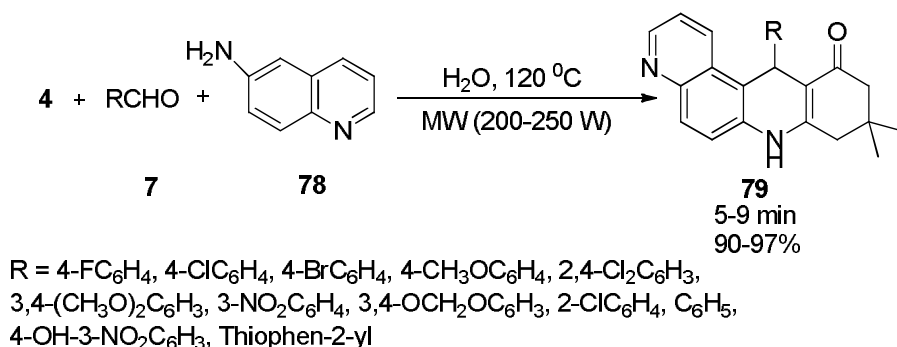
Sangshetti [165] has also introduced oxalic acid (20 mol%) to get **21** in refluxing aqueous media within 60-80 min by 94-97%. The compound **21** has also obtained by Pal and co-workers in the presence of  $\text{Fe}_3\text{O}_4 @ \text{SiO}_2$  nanoparticles (10 mol%), as reusable heterogeneous catalyst, in refluxing water within 15-30 min by 82-95% [166]. Preparation of **21** derivatives has also been done by Amri et al. in 2016 via a domino reaction of aldehydes and dimedone in refluxing water followed by the addition of methyl amine or aniline to the reaction mixture within 5.5-11 h by total yield of 45-67% [167].

Highly efficient synthesis of polyhydroquinoline derivatives **12** were reported by Bandgar group in 2008 via four-component reaction of **6**, **4**, ethyl acetoacetate (**10**), and

ammonium acetate (**11**) in refluxing water within 2.2-8 h by 90-99% [168]. In 2012 Luo group defined tetrabutyl ammonium bromide (TBAB) as an effective promotor for the one-pot synthesis of **12** in green media-water at 85 °C within 3-5 h by 89-96% [169].

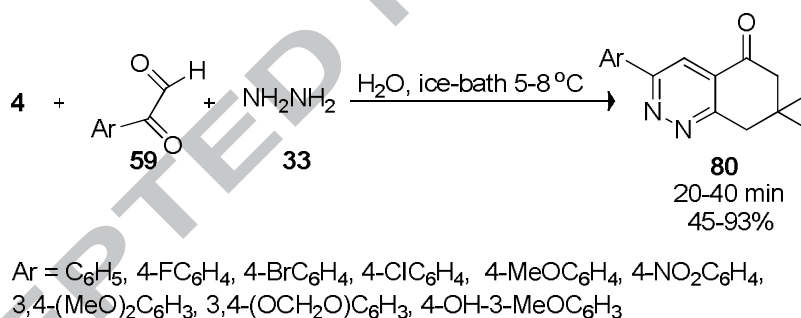
Patil et al. [170] reported one-pot four-component tandem synthesis of hexahydroquinolines (**9**) through the enaminone intermediate using **4**, aryl aldehydes (**7**), **8**, and excess amount of **11**, as both substrate and catalyst, in refluxing water within 57-85 min by 80-90%. Davoodnia and co-workers in 2011 described a convenient route to tetrahydrobenzo[*b*]pyrans (**9**) by a one-pot three-component cyclocondensation of dimedone (**4**), aryl aldehydes (**7**), and malononitrile (**8**) in water using silica gel-supported polyphosphoric acid (PPA-SiO<sub>2</sub>, 0.1 g) as an efficient and reusable catalyst within 8-15 min by 77-93% [171]. PEG-1000 bridged primary amine functionalized dicationic ionic liquid (PA-PEG 1000-DIL)[BF<sub>4</sub>], 0.1 mmol) has also catalyzed preparation of **9** in water at 100 °C within 10-30 min by 86-96% [172]. In 2004, triethylbenzylammonium chloride (TEBA, 0.2 g) provided an efficient access to 3-cyano-substituted 2-amino-4-aryl-4,6,7,8-tetrahydro-5*H*-1-benzopyran-5-ones (**9**) in water at 90 °C within 4-10 h by 82-99% [173]. The compounds **9** have also been got in 2016 in the refluxing aqueous medium in the presence of aspartic acid (10 mol%) within 10-15 min by 88-95% [174]. Khurana and co-workers [176] in 2014 reported 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed one-pot synthesis of **9** in water under reflux conditions within 5-20 min at 60-92%.

Shi et al. [177] reported a series of benzo[*b*][4,7]phenanthrolines (**79**) were synthesized via a catalyst-free three-component reaction of aromatic aldehydes (**7**), 6-aminoquinoline (**78**), and **4** in water at 120 °C under microwave irradiation (ae = 91%, Scheme 39). Compounds with the 4,7-phenanthroline motif which are analogs of ergot alkaloids, possess high and versatile pharmacological effects, such as serotonin antagonism, vasoconstriction, oxytocic and psychotropic activities [178].



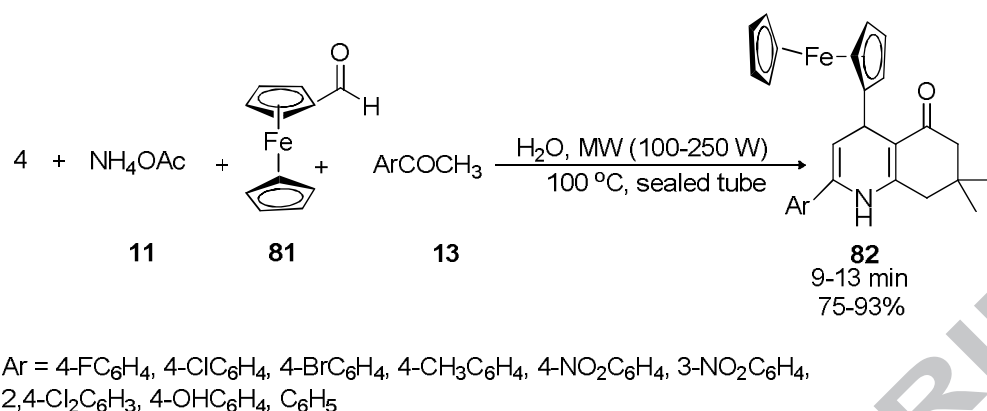
**Scheme 39.** Benzo[*b*][4,7]phenanthrolines.

Rimaz et al. in 2012 [179] investigated a simple regioselective synthesis of new substituted 7,8-dihydrocinnoline-5(6*H*)-ones (**80**) via one-pot three-component reaction of arylglyoxals (**59**) with **4**, and hydrazine hydrate (**33**) in ice water at 5-8 °C in good yields with ae = 82% (Scheme 40). Cinnolines and their derivatives exhibited a broad range of biological activity, such as fungicidal properties [180].



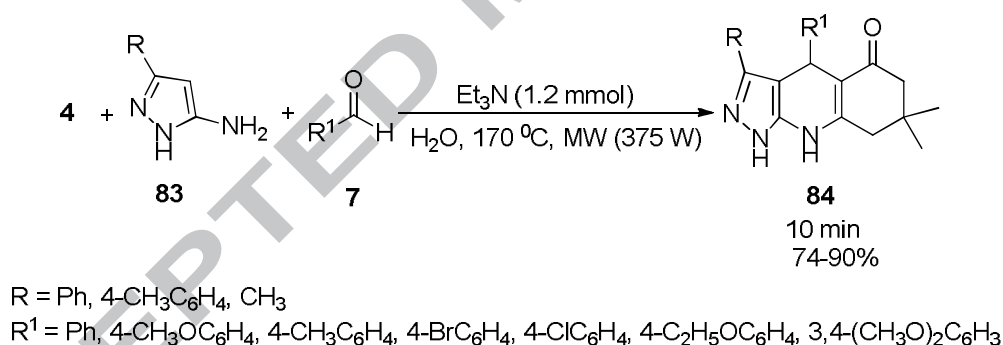
**Scheme 40.** New substituted 7,8-dihydrocinnoline-5(6*H*)-ones.

A clean and expeditious route for the synthesis of 2-aryl-4-ferrocenyl-quinolines (**82**) through microwave-assisted multi-component reaction of ferrocenecarboxaldehyde (**81**) with ketones (**13**), dimedone (**4**), and ammonium acetate (**11**) in water as reaction media at 100 °C is described by Ma and co-workers [181] (ae = 79%, Scheme 41).



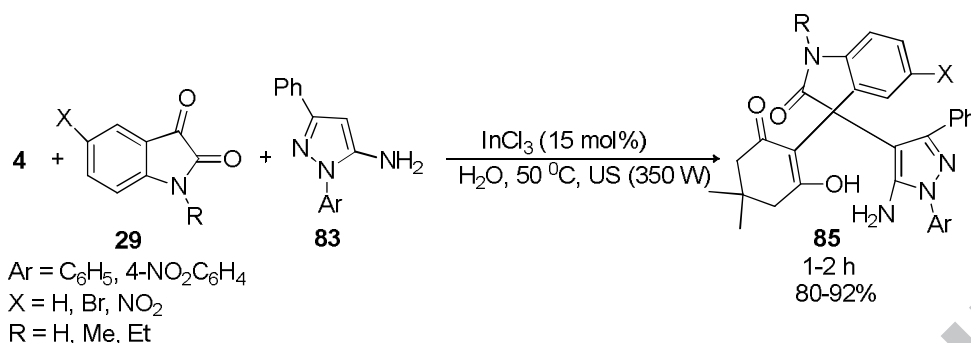
**Scheme 41.** 2-Aryl-4-ferrocenyl-quinolines.

Novel simple and eco-friendly synthetic procedure to obtain pyrazolo[3,4-*b*]quinolin-5-ones (**84**) based on three-component microwaves-assisted heterocyclization reaction of 5-aminopyrazoles (**83**), aromatic aldehydes (**7**), and dimedone (**4**) in hot-water medium at 170 °C was developed (ae = 85%, Scheme 42) [182].



**Scheme 42.** Pyrazolo[3,4-*b*]quinolin-5-ones.

Khorrami et al. [183] in 2010 established Indium(III) chloride as an efficient catalyst for the synthesis of 3-(5-amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones (**85**) by one-pot, three-component reaction of dimedone (**4**), 1*H*-pyrazol-5-amines (**83**), and isatins (**29**) in water under ultrasound irradiation at 50 °C (ae = 96%, Scheme 43).

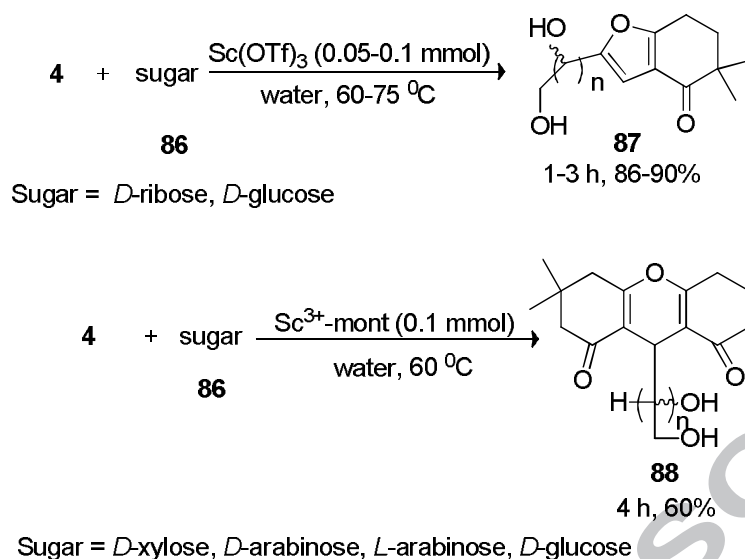


**Scheme 43.** 3-(5-Amino-1*H*-pyrazol-4-yl)-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-ones.

Azzam et al. in 2012 reported a convenient method for the synthesis of octahydro-quinazolin-2,5-diones (**18**) by the reaction of aromatic aldehydes (**7**), dimedone (**4**), and urea (**16**) in the presence of  $\text{SiO}_2\text{-NaHSO}_4$  (0.1 g) as an efficient, mild, and recyclable heterogeneous catalyst in water at 60-80 °C within 1-2 h by 85-95% [184]. They have also obtained by Hassani and co-workers [185] in 2006 according to the Biginelli reaction in the presence of two drops of concentrated  $\text{H}_2\text{SO}_4$  in refluxing water in 3 h by 90-98%.

The condensation of dimedone (**4**) with unprotected sugars (**86**) in aqueous solution at 60 °C in the presence of a catalytic amount of scandium cation-exchanged montmorillonite ( $\text{Sc}^{3+}\text{-mont}$ ) gave 9-hydroxyalkyl-3,3,6,6,-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-diones (**87**) in good yields with the ae = 89%, while the use of  $\text{Sc}(\text{OTf})_3$  instead of  $\text{Sc}^{3+}\text{-mont}$  gave the hydroxyalkyl-6,7-dihydrobenzofuran-4(5*H*)-one derivatives (**88**) in good yields (ae = 86%) via the direct C-glycosylation process (Scheme 44) [186].





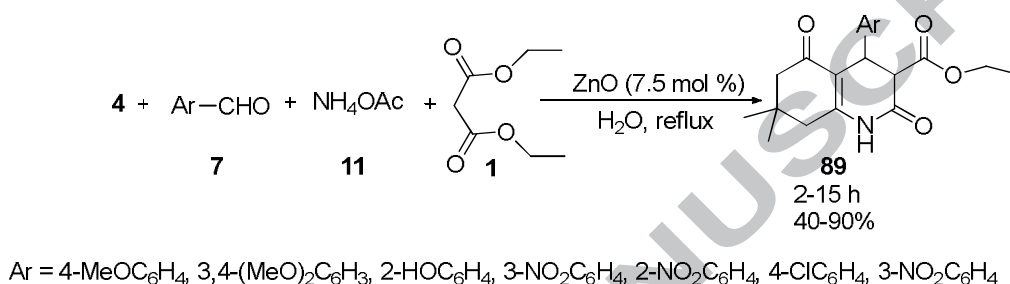
**Scheme 44.** 9-Hydroxyalkyl-3,3,6,6,-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-diones and hydroxyalkyl-6,7-dihydrobenzofuran-4(5*H*)-one derivatives.

A novel nanospherical ordered mesoporous Lewis acid polymer ( $\text{Sc(OTf)}_2\text{-NSMP}$ ) has been prepared in 2014 by functionalizing the mesoporous phenol-formaldehyde polymer framework with scandium triflate groups. The solid acid catalyst (0.1 mmol) has been catalyzed the C-glycosylation reaction between various monosaccharides (**86**) and dimedone (**4**) in water at 100 °C to obtain xanthone glycosides (**88**) within 48 h by 56-92% [187].

Satto et al. in 2007 claimed that the reaction of *D*-ribose (**86**) with dimedone (**4**) which catalyzed by scandium cation-exchanged montmorillonite ( $\text{Sc}^{3+}\text{-mont}$ , 0.1 mmol) afforded hydroxyalkyl-3,3,6,6,-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**87**) in water at 60 °C within 4 days by 86% yield, where utilizing scandium triflate gave hydroxyalkyl-6,7-dihydrobenzofuran-4(5*H*)-one derivatives (**88**) by 78% in a 4 day period under the same conditions [188]. The different selectivity between  $\text{Sc}^{3+}\text{-mont}$  and  $\text{Sc(OTf)}_3$  has been rationalized by the mechanism of the transformation; while the  $\text{Sc(OTf)}_3$  catalyzed reaction in water through the classical mechanism, when  $\text{Sc}^{3+}\text{-mont}$  is used the

compounds are reacting when coordinated to the Sc center in the silicate layer of  $\text{Sc}^{3+}$ -mont, gave rise to the addition of two molecules of dimedone [189].

In 2012 ZnO has been shown to be an inexpensive, efficient and mild catalyst for a one-pot four-component synthesis of some novel octahydroquinolindione-3-carboxylic acid ethyl esters (**89**) using diethylmalonate (**1**), dimedone (**4**), ammonium acetate (**11**), and appropriate aromatic aldehydes (**7**) in refluxing water (ae = 71%, Scheme 45) [190].



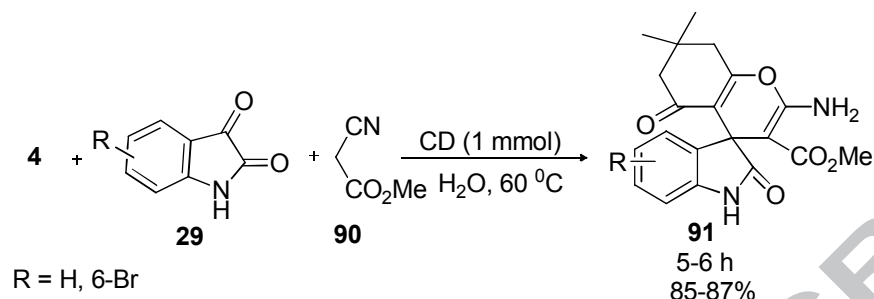
**Scheme 45.** Octahydroquinolindione-3-carboxylic acid ethyl esters.

Kumar et al. [191] reported thiourea dioxide (TUD, 2 mol%) in heated water at 50 °C as reusable organocatalytic system for the one-pot synthesis of polyhydroquinoline derivatives (**12/ 66**) *via* the Hantzsch-type coupling of aldehyde (**7**), dimedone (**4**), acetoacetates (**10/ 65**), and **11** at 50 °C by 85-94%.

The compounds **30** have been achieved at 80 °C aqueous media in the presence of a glutathione grafted nano-organocatalyst (nano-FGT), within 15 min by 90-97% yield [192]. The catalyst could be used during 8 cycles without activity loss. The Knoevenagel condensation followed by Michael addition in the presence of  $\text{Mg}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  (5 mol%) in refluxing water within 25-120 min by 75-95% has also yielded **30** reported by Boumoud et al. [193]

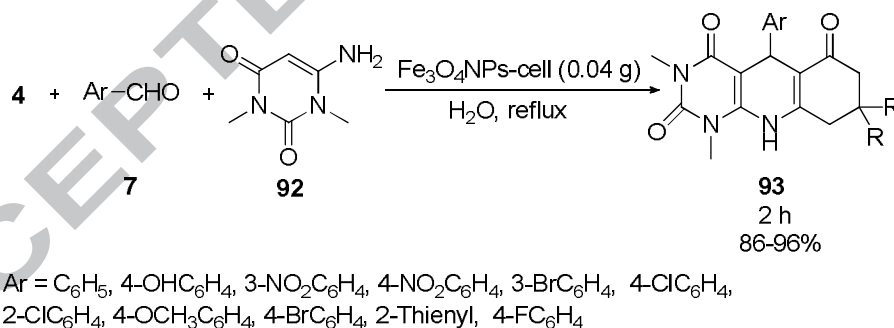
A neutral and efficient one-pot three-component aqueous-phase preparation route was demonstrated for various spirooxindole derivatives (**91**) from isatins (**29**),

cyanomethylacetoacetate (**90**), and **4** by supramolecular catalysis involving  $\beta$ -cyclodextrin (CD) in water at 60 °C (Scheme 46) [194].



**Scheme 46.** Spirooxindole derivatives.

Three-component reaction of several aromatic aldehydes (**7**), 6-amino-1,3-dimethyluracil (**92**), and **4** in H<sub>2</sub>O as a green solvent under reflux conditions using Fe<sub>3</sub>O<sub>4</sub> nano-particles supported on cellulose (Fe<sub>3</sub>O<sub>4</sub> NPs-cell), after 2 h gave pyrimido[4,5-*b*]quinolones (**93**) in high yields with atom economy of 91% (Scheme 47) [195]. Some functionalized pyrimidines have also been identified as a new class of fibroblast growth factor receptor (FGFR3) tyrosine kinase inhibitors [196].



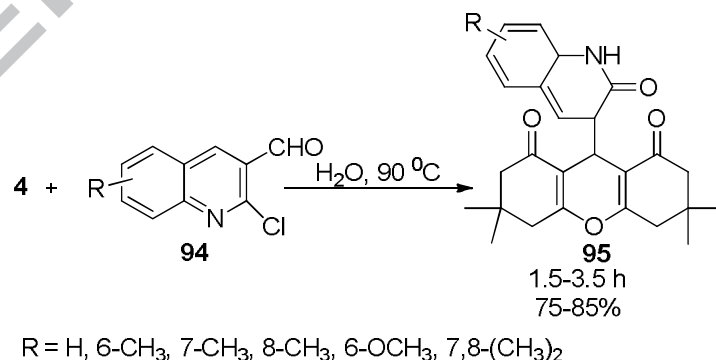
**Scheme 47.** Pyrimido[4,5-*b*]quinolones.

In 2007 molecular iodine (10 mol%) has been used as efficient catalyst for an improved and rapid one-pot synthesis of 2,2-arylmethylenebis(3-hydroxyl-5,5-dimethyl-2-cyclohexen-1-one) (**37**) in water at 100 °C within 20-25 min by 89-97% [197].

The 1,8-dioxo-octahydroxanthenes (**15**) has been prepared by Ganesan group by  $\text{ZnCl}_2$  (0.125 mmol) in water at 120 °C efficiently in 45-180 min by 75-97% [198]. These compounds has also been gained by Sharma et al. in 2016 in the presence of  $\text{Cs}_2.5\text{H}_{0.5}\text{PW}_{12}\text{O}_{40}$  (5 mol%) in refluxing water within 15-125 min by 72-96% yield [199].

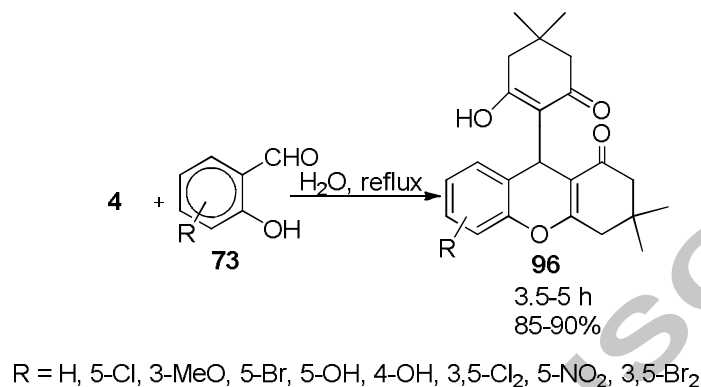
( $\text{Zn}[(L)\text{Proline}]_2$ , 2 mol%) in refluxing water in 0.5 h by 63-97% [200], silica-supported preyssler nano particles (SPNP, 0.05 mmol) in 3 h by 82-96% in refluxing water by Javid et al. [201], EPZ-10 (10 mol%), as a heterogeneous clay catalyst, in heated water at 70 °C via a domino Knoevenagel/ hetero-Michael-addition reaction within 2-3 h by 80-95% by Pore et al. [202], catalyst-free 80 °C aqueous media examined by Kumaresan et al. in 2014 within 10 min by 80-84% [203] are other systems to obtain **15**. In the later procedure the authors investigated the self-catalyzed Bronsted-Lowry acid catalytic behavior by both experimental and theoretical methods.

A facile and benign method for the preparation of 3,4,6,7-tetrahydro-9-(1,2-dihydro-2-oxoquinolin-3-yl)-2*H*-xanthene-1,8(5*H*,9*H*)-diones (**95**) from substituted 2-chloro-3-formylquinoline (**94**) and **4** in water at 90 °C using parallel synthesizer is reported. The present methodology offered a tandem-cascade methodology, high yield with ae = 88%, and operational simplicity (Scheme 48) [204].



**Scheme 48.** 3,4,6,7-Tetrahydro-9-(1,2-dihydro-2-oxoquinolin-3-yl)-2*H*-xanthene-1,8(5*H*,9*H*)-diones.

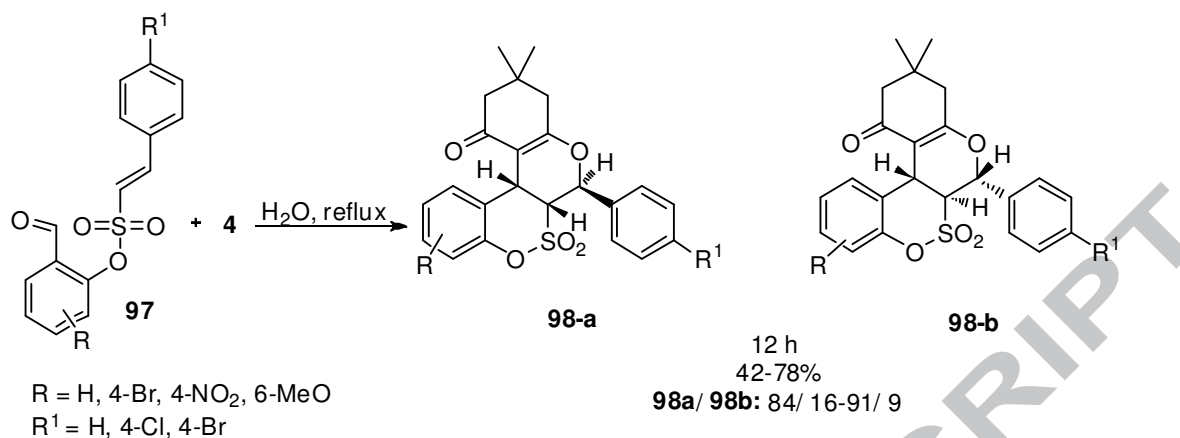
An eco-friendly synthesis of 1-oxo-hexahydroxanthenes (**96**) has been expediently accomplished by Pore et al. in 2010 via the reaction of salicylaldehydes (**73**) with **4** in water as universal solvent at reflux conditions without a catalyst (ae = 91%, Scheme 49) [205].



**Scheme 49.** Synthesis of 1-oxo-hexahydroxanthenes.

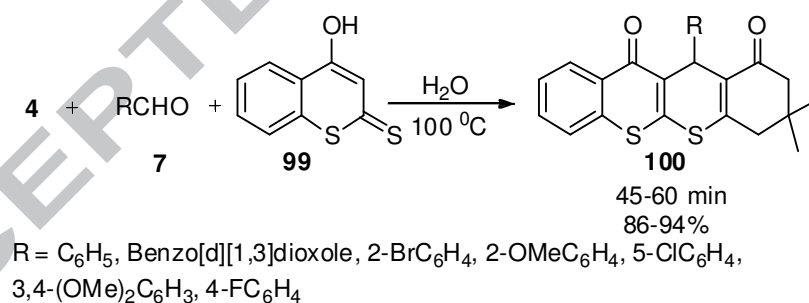
Cerium(III) chloride heptahydrate (CeCl<sub>3</sub>·7H<sub>2</sub>O) is another promoter reported by Sabitha et al. to catalyze preparation of **96** derivatives in refluxing aqueous media within 1.5-5 h by 82-96% [206].

Ghandi and co-workers [207] in 2011 described preparation of domino Knoevenagel-hetero-Diels-Alder cycloadducts of novel hexahydro-chromene (**98**) using dimedone (**4**) and sulfonates (**97**) in water under reflux via an efficient catalyst-free, diastereoselective procedure (Scheme 50). The bifunctional starting materials which contain an aldehyde and an unsaturated sulfonate, has been obtained by the reaction of 2-hydroxybenzaldehyde and (*E*)-2-phenylethenesulfonyl chloride in the presence of K<sub>2</sub>CO<sub>3</sub> in acetone at room temperature with atom economy of 96%.



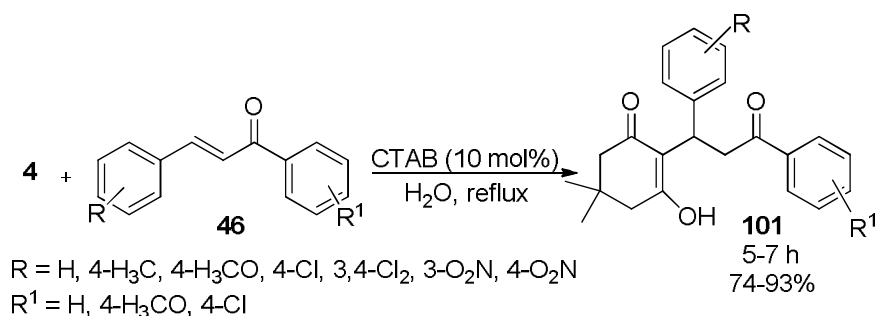
**Scheme 50.** Novel hexahydro-chromenes.

Majumdar et al. [208] developed a synthetic route for various dihydrothiochromeno[2,3-*b*]thiochromene derivatives (**100**) by the domino reaction of 4-hydroxy-2*H*-thiochromene-2-thione (**99**), aldehydes (**7**), and dimedone (**4**) in water at 100 °C (Scheme 51). The significant advantages of this protocol in addition with short reaction time, excellent yields, and *ae* = 86%, is formation of three new bonds and a stereocenter in one operation from easily available starting materials.



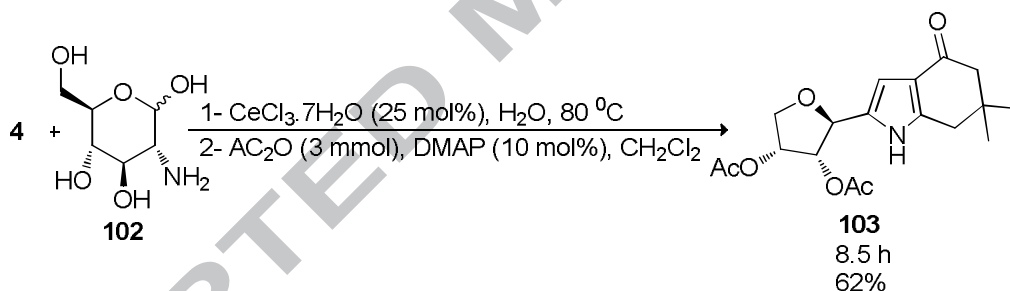
**Scheme 51.** Synthesis of various dihydrothiochromeno[2,3-*b*]thiochromenes.

Wang et al. [209] demonstrated the reaction of dimedone (**4**) with chalcones (**46**) in refluxing water mediated by cetyltrimethylammonium bromide, gave the expected Michael adducts (**101**) in good to excellent yields and *ae* = 99%, after purification by column chromatography with petroleum ether/ ethyl acetate (3:1) (Scheme 52).



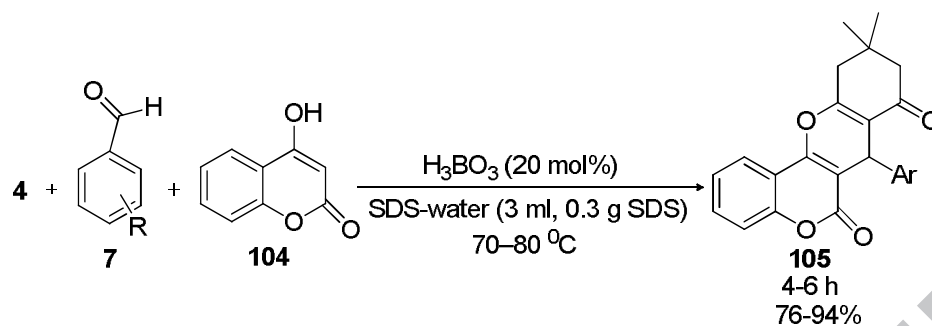
**Scheme 52.** Michael adducts of dimedone with chalcones.

The coupling reaction of *D*-glucosamine (**102**) with dimedone (**4**) in the presence of CeCl<sub>3</sub>·7H<sub>2</sub>O in water at 80 °C, which followed by acetylation by acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) in CH<sub>2</sub>Cl<sub>2</sub>, to furnish C-pyrrolyl glycosides (**103**) in good to high yields has been reported by Subba Reddy et al. in 2011 (Scheme 53) [210].



**Scheme 53.** C-pyrrolyl glycosides.

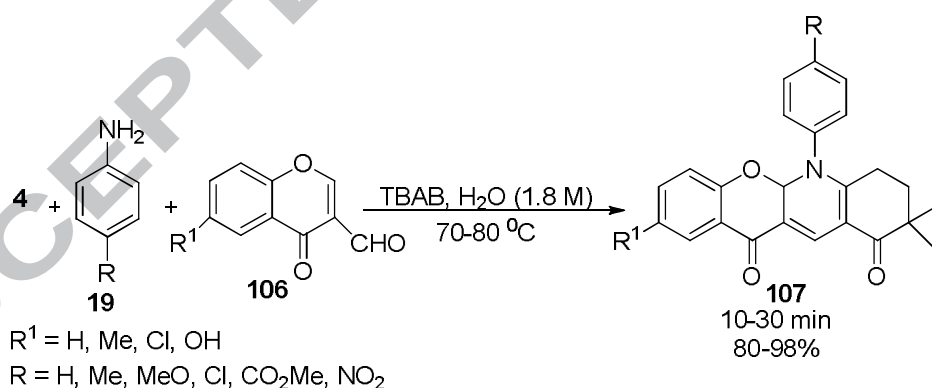
Ganguly et al. [211] in 2014 described synthesis of 7-arylbenzopyrano[4,3-*b*]benzopyran-6,8-diones (**105**) through the three-component reaction of 4-hydroxycoumarin (**104**), aromatic aldehydes (**7**), and dimedone (**4**) with boric acid catalyst under aqueous micellar conditions (utilizing SDS) at 70-80 °C (ae = 91%, Scheme 54).



R = H, 3-NO<sub>2</sub>, 4-MeO, 4-Cl, 4-NO<sub>2</sub>, 4-OCHCH<sub>2</sub>-3-MeO, 3-(2-OCHCHCH<sub>3</sub>),  
 Cinnamaldehyde, Thiophene-2-carbaldehyde, Benzo[d][1,3]dioxole-5-carbaldehyde

**Scheme 54.** Synthesis of 7-arylbenzopyrano[4,3-*b*]benzopyran-6,8-diones.

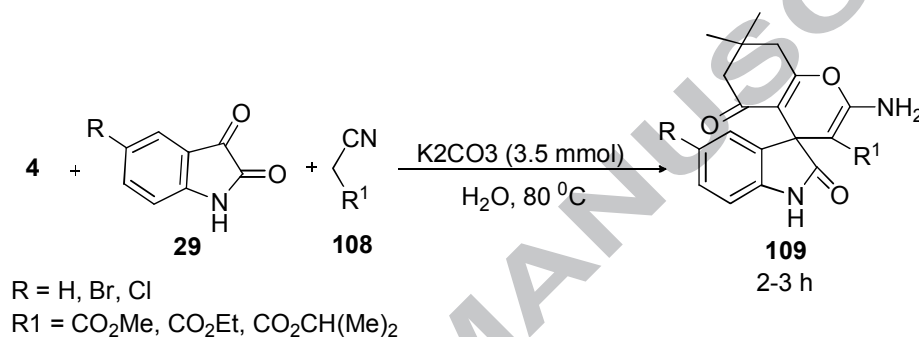
An efficient and green synthesis of hitherto unreported 5-aryl-3,3-dimethyl-2,3-dihydro-5*H*-chromeno[2,3-*b*]quinoline-1,11(4*H*,5*H*)diones (**107**) has been accomplished by a three-component reaction involving chromone-3-carbaldehyde (**106**), an aromatic amine (**19**), and dimedone (**4**) in 1.8 M aqueous tetrabutylammonium bromide (TBAB) solution at 70-80 °C (ae = 91%, Scheme 55) [212]. Chromenoquinolines exhibited various activities depending on the nature of fusion between the chromone and quinoline rings. They act as potent antiinflammatory agents [213].



**Scheme 55.** 5-Aryl-3,3-dimethyl-2,3-dihydro-5*H*-chromeno[2,3-*b*]quinoline-1,11(4*H*,5*H*)diones.



In 2014 Abadi and co-workers have reported an environment-friendly procedure for the Preparation of some alkyl 2'-amino-2-oxospiro[indoline-3,4'-pyran]-3'-carboxylates (**109**) through the one-pot reaction of **4**, isatins (**29**), and cyanoacetic esters (**108**) in the presence of potassium carbonate in heated aqueous media. The average atom economy of the procedure is 95.6%. The authors also investigated the behavior of the obtained compounds (**109**) against two cancer cell lines, namely HT-29 and MDA-231, which confirm their potent anti-tumor properties (Scheme 56) [214].



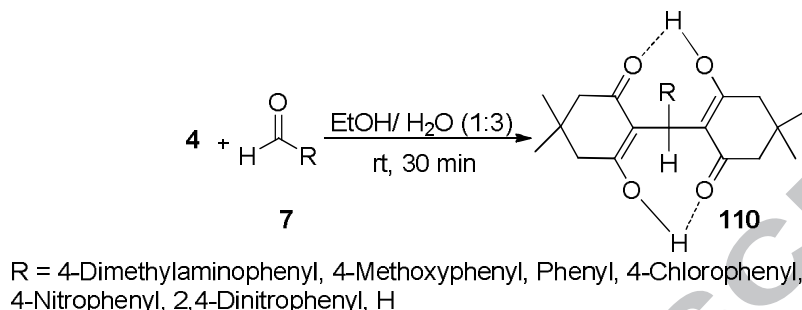
**Scheme 56.** Alkyl 2'-amino-2-oxospiro[indoline-3,4'-pyran]-3'-carboxylates.

#### 4. The reactions of dimedone in a mixed aqueous-organic media

##### 4.1. The reactions of dimedone in a mixed aqueous-organic solvent at room temperature

Ferreira et al. [215] in 2014 reported 2,2'-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones) with para and ortho-R groups on the benzene ring were prepared and studied by nuclear magnetic resonance (NMR) and molecular modeling to determine their conformational exchanges. Experimental and calculated results indicated conformational interconversions in these compounds by rotation of benzene ring and slow movement of dimedone rings, leading to intramolecular hydrogen bond length variation. The presence of one R group at the ortho position on the benzene ring modifies conformational exchange, leading to disappearance of one intramolecular hydrogen bond and superposition of diverse

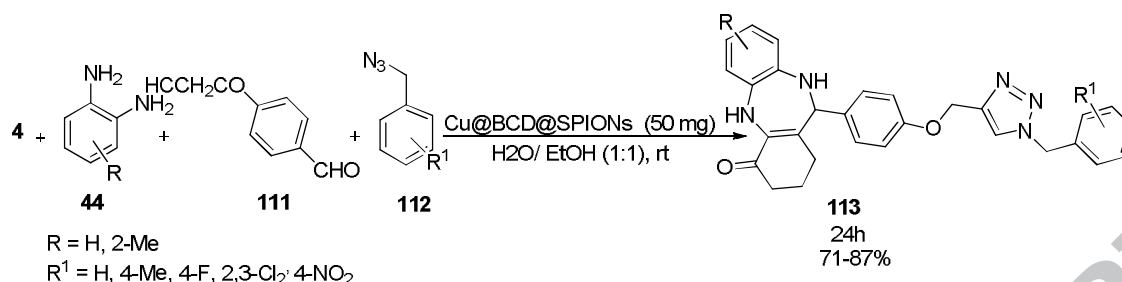
NMR signals (Scheme 57). These results will be used to study the interaction of these compounds with bio-molecules and their use as starting materials for design and synthesis of new bioactive agents.



**Scheme 57.** 2,2'-Arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-ones).

Tu and co-workers [216] in 2005 identified a series of new *N*-cyclopropyldecahydroacridine-1,8-dione derivatives (**20**) via the one-pot reaction of aromatic aldehydes (**7**), **4** and cyclopropanamine (**19**) in solution of glycol and water (1:2) under microwave irradiation at room temperature in the presence of sodium acetate (2 mmol) within 5-10 min by 78-94% yield. It is interesting to mention that in 2004 Tu and co-workers prepared one derivative of the titled products via the reaction of dimedone with 3-methoxy-4-hydroxybenzaldehyde, cyclopropylamium chloride and NaOAc in glycol and water and studied its X-Ray analysis [217].

A novel and one-pot synthetic approach was introduced to get novel 1-benzyl-1*H*-1,2,3-triazoldibenzodiazepinones (**113**) through a click reaction of **4**, *o*-phenylenediamines (**44**), 4-propargyloxybenzaldehyde (**111**), and azidomethylbenzenes (**112**) using [Cu@ $\beta$ -CD@SPIONs] as a green catalyst. The efficient and recoverable copper catalyst was prepared by the immobilization of Cu into  $\beta$ -cyclodextrin covalently attached to magnetic nanoparticles (denoted as [Cu@ $\beta$ -CD@SPIONs]) (Scheme 58) [218]



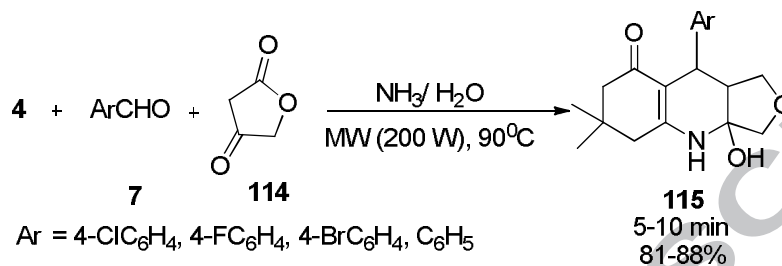
**Scheme 58.** 1-Benzyl-1*H*-1,2,3-triazoldibenzodiazepinones.

#### 4.2. The reactions of dimedone in a heated mixed aqueous-organic media

Sabitha et al. [219] reported an efficient one-pot synthesis of 4*H*-benzo[*b*]pyrans (**9**) via a three-component cyclocondensation of **7**, malononitrile (**8**), and **4** using CeCl<sub>3</sub>·7H<sub>2</sub>O (10 mol%) as catalyst in 1:2 mixture of water/ ethanol under reflux conditions to afford the products within 1-2 h by 70-94% yield. In addition with the benzaldehydes derivatives furan-2-carbaldehyde have also performed the reaction well. Caro's acid supported on silica gel (CA-SiO<sub>2</sub>, 0.16 mmol) in ethanol/ water (2:5) under reflux conditions within 15-20 min by 92-95% by Heravi et al. in 2011 [220], in addition with Ce(SO<sub>4</sub>)<sub>2</sub>·4H<sub>2</sub>O (2.5 mol%) in a refluxing equimolar ration of ethanol/ water at 45 °C [221] and Lactose (40 mol%) in H<sub>2</sub>O/ EtOH (3:1) at 60 °C [222] are other catalytic systems utilized to obtain **9**. *N,N*-diethylamino-propylated silica (NDEAP, 0.1 eq) in an equimolar amount of water and ethanol mixture under microwave irradiation (100 W) at 25-80 °C within 5-37 min by 12-93% yield also gained **9**. The temperature was ramped from rt to 80 °C which was monitored by radiation thermometer [223].

Narayanan et al. [224] described three-component one-pot synthesis of octahydroquinazolinone (**18**) catalyzed by vanadium *n*-propylamino phosphate (VNPRP, 0.05 g) through the reaction of **4** with aldehydes (**7**), and urea (**16**) or thiourea (**17**) in 1:1 water/ methanol mixture under reflux conditions to afford the products within 90-180 min by 30-85%

An unexpected and green synthesis of azapodophyllotoxins (**115**), was realized via microwave-assisted multi-component reactions of dimedone (**4**), tetronic acid (**114**) and aromatic aldehydes (**7**) in ammonia water at 90 °C (Scheme 59) [225]. Azapodophyllotoxin derivatives are well-known anticancer agents [226].



**Scheme 59.** Azapodophyllotoxin derivatives.

## 5. Conclusion

In this review report, different types of reactions which included dimedone as substrate have been presented. The mentioned concise reactions, have been classified based on the reaction media. This focus is due to the importance of economical and green transformations in organic synthesis. According to the whole report, the reaction could occur under solvent-free conditions, in aqueous media, and in the presence of various organic solvents. Some cases needed heat to accelerate them and some others take place in room temperature. The authors hope this classified report up to 2016 would lead the general readers to a strong interest for utilizing dimedone in a vast range of transformations with a centralization on their medium.

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