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Review

Importance of Hybrid Catalysts toward the Synthesis of 5*H*-Pyrano[2,3-*d*]pyrimidine-2-ones/2,4-diones (Thiones)

Mehul P. Parmar, Ruturajsinh M. Vala, and Hitendra M. Patel*

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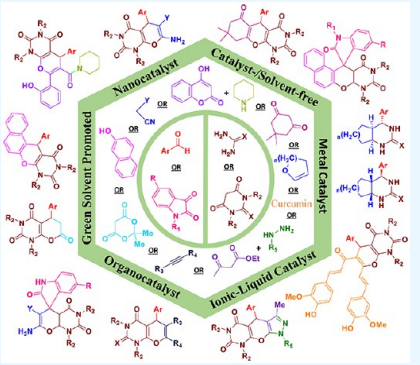
ABSTRACT: The pyranopyrimidine core is a key precursor for medicinal and pharmaceutical industries due to its broader synthetic applications as well as its bioavailability. Among its four possible isomers, we found that 5*H*-pyrano[2,3-*d*]pyrimidine scaffolds have a wide range of applicability, and in recent years, they have been intensively investigated, but the development of the main core is found to be more challenging due to its structural existence. In this review article, we cover all of the synthetic pathways that are employed for the development of substituted 4-aryl-octahydropyrano/hexahydrofuro[2,3-*d*]pyrimidin-2-one (thiones) and 5-aryl-substituted pyrano[2,3-*d*]pyrimidindione (2-thiones) derivatives through a one-pot multicomponent reaction using diversified hybrid catalysts such as organocatalysts, metal catalysts, ionic liquid catalysts, nanocatalysts, green solvents, catalyst-/solvent-free conditions, and miscellaneous catalysts as well as the mechanism and recyclability of the catalysts. This review mainly focuses on the application of hybrid catalysts (from 1992 to 2022) for the synthesis of 5*H*-pyrano[2,3-*d*]pyrimidine scaffolds. This review will definitely attract the world's leading researchers to utilize broader catalytic applications for the development of lead molecules.



1. INTRODUCTION

In recent years, heterocyclic scaffolds have achieved importance in medicinal chemistry, active pharmaceutical ingredient industries, pharmaceutical industries, agrochemicals, and natural products. Heterocyclic compounds are cyclic organic scaffolds that encompass at least one heteroatom such as nitrogen, oxygen, and sulfur, which are the most common heteroatoms. However, other heteroatoms consisting of heterocycles are also known.[1,2] Aliphatic heterocyclic compounds and aromatic heterocyclic compounds are two subgroups of heterocyclic compounds.[1] Among them, aromatic heterocyclic scaffolds have gained much interest in academic research laboratories, chemical, and pharmaceutical industries to frame novel drug motifs, insecticides, and natural products. As fused heterocyclic compounds are conspicuous segments of heterocyclic compounds, pyranopyrimidine is a fused heterocyclic moiety that represents a superior combination along with other fused heterocycles in which a pyran ring is fused with a pyrimidine ring in which two nitrogen atoms are present at first and third positions and an oxygen atom is present at the eighth position.[3] In synthetic organic chemistry, one-pot reactions are an efficient approach to synthesize 5*H*-pyrano-[2,3-*d*]pyrimidine-2-ones/2,4-diones (thiones) in the same reaction vessel.[4] Multicomponent reactions provide a synthetic route to afford the desired product, which involves the use of three or more starting materials and allows carbon−carbon and carbon−heteroatom bond formation in a single operation, which is helpful in the development of bioactive scaffolds.[5,6]

Nowadays, green chemistry has received prominent interest in research fields and replaces toxic and hazardous materials with green and environmentally friendly reagents and solvents. "*Green chemistry is an area of chemistry focused on the designing of products and processes that minimizes or eliminates the use and generation of hazardous substances (USEPA, 2006)*".[7] The possible isomers[8] of pyranopyrimidines are shown in Figure 1.

Among the four possible isomers of pyranopyrimidine, 5*H*-pyrano[2,3-*d*]pyrimidine scaffolds have been intensively investigated in recent times owing to their huge applicability, but the development of the main core is found to be more challenging due to its structural existence. Pyrano[2,3-*d*]pyrimidine derivatives showed a wide range of biological and pharmacological activities including antitumor,[9,10] antibacterial,[11] antimicrobial,[10] antioxidant,[12] antifungal,[13] vasodilator, anti-inflamatory,[14] antidiabetic,[15] and cardiotonic[16] activities. Moreover, several of these compounds have also been studied as nonlinear optical materials and dyes.[17] Some of the bioactive pyrano[2,3-*d*]pyrimidinones are shown in Figure 2.

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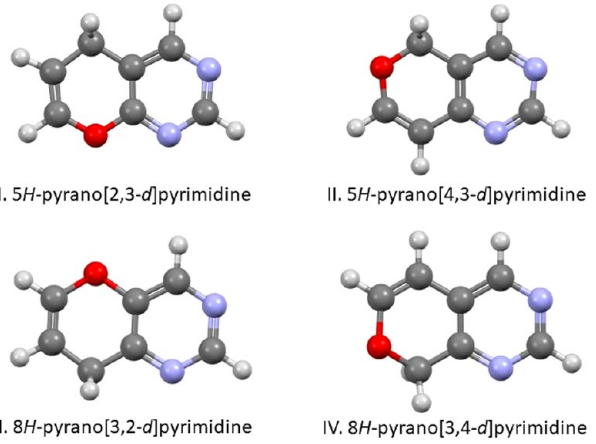

Figure 1. Four possible isomers of pyranopyrimidines.

In addition, pyrano[2,3-*d*]pyrimidines often show antimicrobial activity[18] with IC_{50} values of 257 and 278 mM for 2-chloro and 2-nitro derivatives, respectively (Figure 2, VII), cytotoxic activity against the HeLa cell line with an IC_{50} of 129 mM (Figure 2, VIII), urase inhibitory activity[19] with an IC_{50} value 106.29 mM (Figure 2, IX), and α-amylase and α-glucosidase inhibitory activity[20] with an IC_{50} value of 6.490 mM (Figure 2, X). This encourages the world's leading researchers to utilize broader catalytic applications for the development of lead molecules. Gore and Rajput[21] reported on the pyrimidine core synthesis, and Bhat et al.[22] also reported on bioactive annulated pyrimidine derivatives. Recently, Elattar et al.[23] reported on the pyrano[2,3-*d*]pyrimidine core. These reported review articles lack many synthetic approaches for pyrano[2,3-*d*]pyrimidine. So, this inspired us to report a new review article on the synthesis of 5*H*-pyrano[2,3-*d*]pyrimidine-2-ones/2,4-diones (thiones). In this review article, we focus on various leading edge studies of the one-pot multicomponent synthesis of discrete 5*H*-pyrano[2,3-*d*]pyrimidine-2-ones/2,4-dione (thione) scaffolds, namely, 4-aryl-substituted octahydropyrano/hexahydrofuro[2,3-*d*]pyrimidin-2-one (thione) [**TS-1**] and 5-aryl-substituted pyrano[2,3-*d*]pyrimidindione (thione and trione) [**TS-2**] derivatives by utilizing various hybrid catalysts such as organocatalysts, heterogeneous or homogeneous metal catalysts, ionic liquid catalysts, nanocatalysts, green solvents, catalyst-/solvent-free conditions, and miscellaneous catalysts along with the mechanism and recyclability of the catalyst. Some of the privileged 5*H*-pyrano[2,3-*d*]pyrimidine-2-one (thione)/2,4-dione scaffolds covered within this review are shown in Figure 3.

2. SYNTHESIS OF 4-ARYLOCTAHYDROPYRANO/HEXAHYDROFURO[2,3-*d*]-PYRIMIDIN-2-ONES (THIONES)

In the last 15 years, much more attention has been given to the synthesis of substituted 4-aryl octahydropyrano/hexahydrofuro[2,3-*d*]pyrimidin-2(8a*H*)-ones/thiones (**TS-1**). In this section, we cover the synthetic methodologies that were employed by different research groups. 4-Phenyloctahydropyrano[2,3-*d*]pyrimidin-2(8a*H*)-ones/thiones were synthesized by Zhu et al.[24] with the generation of three chiral

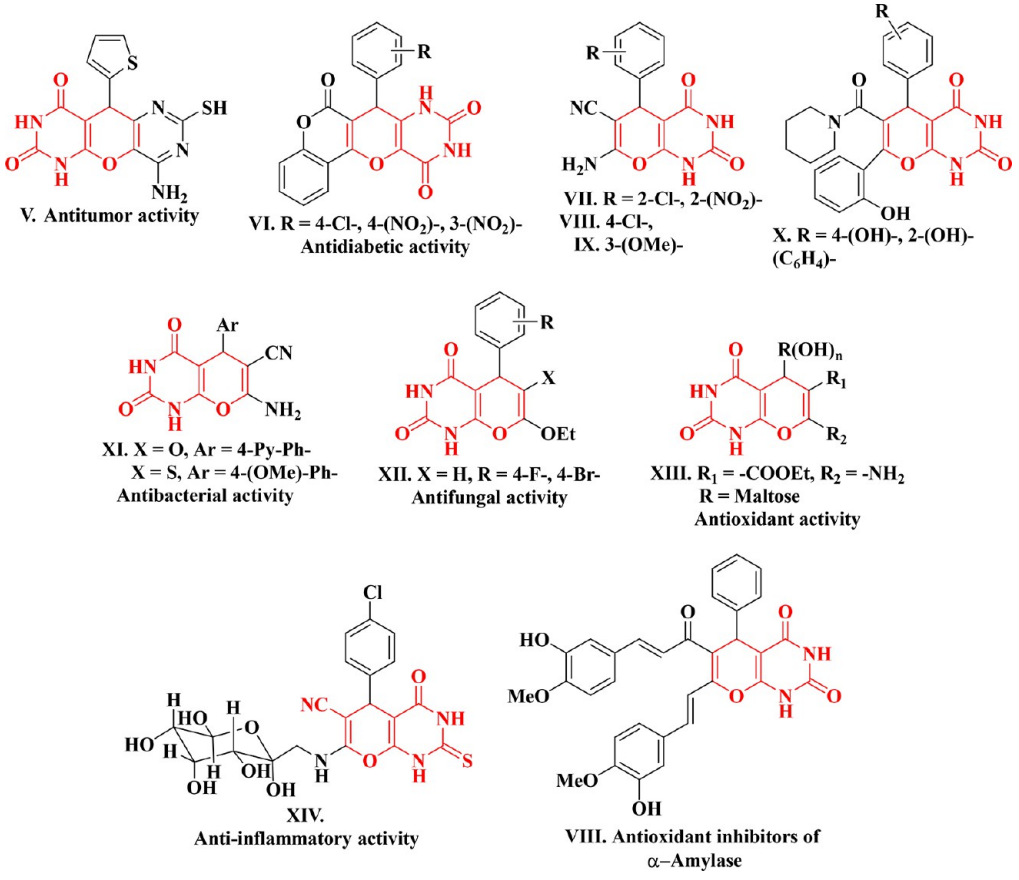

Figure 2. Some of the bioactive pyrano[2,3-*d*]pyrimidine dione/triones.

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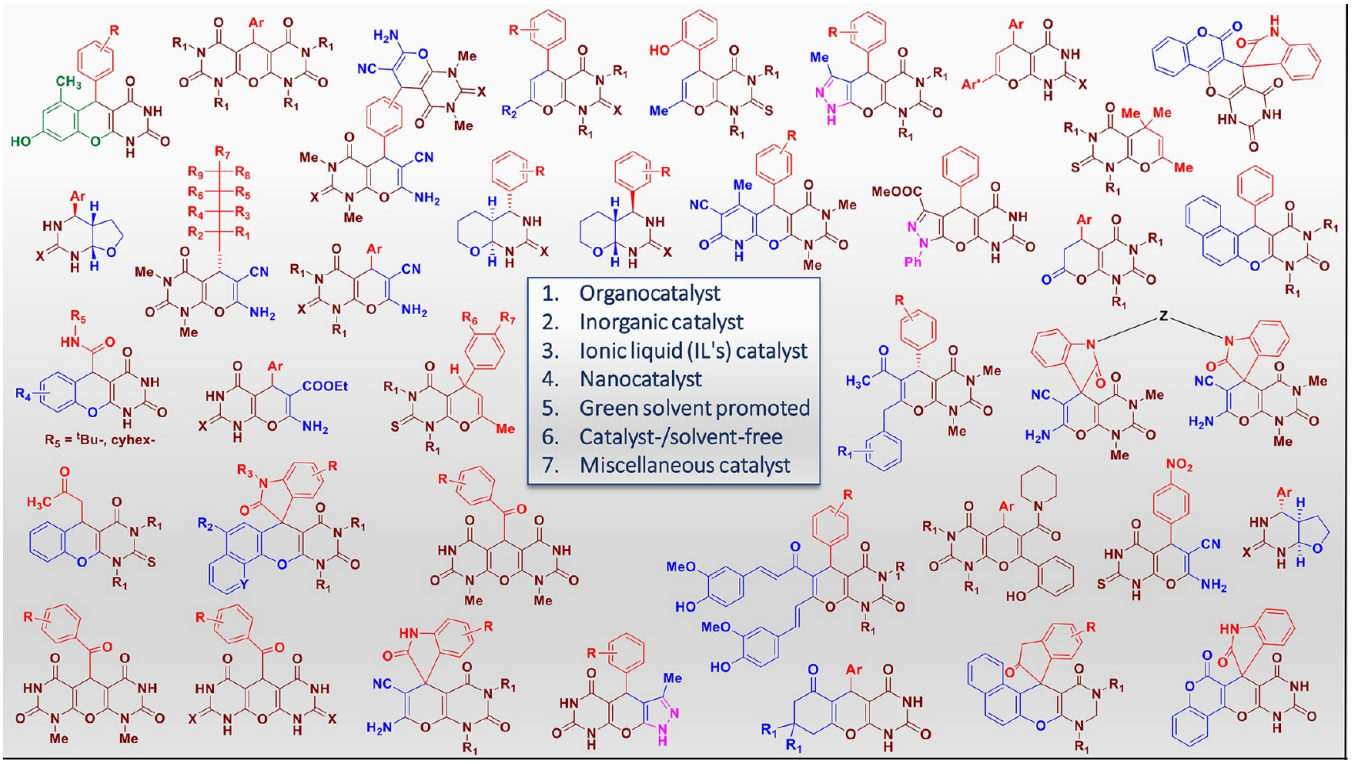

Figure 3. Some of the privileged 5*H*-pyrano[2,3-*d*]pyrimidine-2-one (thione)/2,4-dione scaffolds covered in this review.

centers, and all are cis to each other. Pandey et al.[25] also synthesized them using an organocatalyst. The usual strategies involved the synthesis of **TS-1** and its various analogues with excellent diastereoselectivity through the single-pot three-component reaction of discrete aromatic aldehydes with urea/thiourea and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the presence of an appropriate catalyst as well as a solvent. Various synthetic routes that were used by different groups using different catalysts are described in Figure 4.

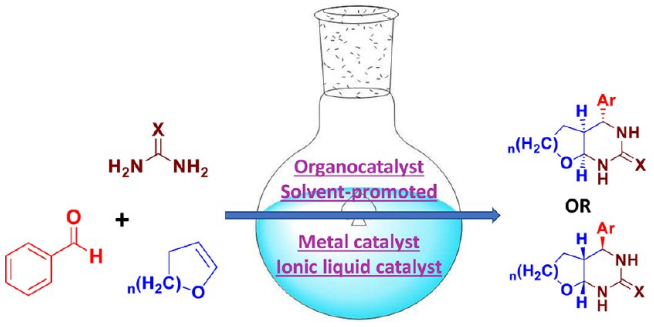

Figure 4. Discrete synthetic routes to afford the targeted scaffold **1** using an organocatalyst, solvent-promoted, metal catalyst, and an ionic-liquid catalyst.

2.1. Organocatalyzed Synthesis of TS-1. In organocatalyzed reactions, organic acids and bases, such as L-proline, *p*-toluene, sulfonic acid, etc., can be used as a catalyst. In this regard, Tripathi et al.[25] also reported the synthesis of 4-aryloctahydro-1*H*-pyrano[2,3-*d*]pyrimidine-2(8a*H*)-ones/thiones **4**. The three-component reaction of aromatic aldehyde **1** (1 equiv), urea/thiourea **2** (1.5 equiv), and 3,4-dihydro-(2*H*)-pyran **3** (1 equiv) proceeded in the presence of L-proline as a Lewis acid organocatalyst, trifluoroacetic acid (TFA) as a cocatalyst, and acetonitrile (CH_3CN) as solvent at 85 °C under reflux conditions (Scheme 1). In the absence of TFA, only a complex mixture was obtained. The entire aldehyde was consumed within 7 h, and the product formation was achieved by the appearance of a solid which was crystallized from ethanol to get the pure product.

Kantevari et al.[26] also reported a Biginelli-type *para*-toluene sulfonic acid (*p*-TSA)-catalyzed highly diastereoselective synthesis of analogues of **TS-1**, i.e., **4a**, with the same substrate scope using *p*-TSA catalyst in a DMF/CH_3CN solvent mixture under reflux (Scheme 1). A variety of substituted aryl/heteryl aldehydes with either electron-withdrawing groups (EWGs) or electron-releasing groups (ERGs) gave a high yield of product **4a**. The major advantages of using this method involved easy availability of the catalysts, an environmentally friendly procedure for the generation of a combinatorial library of DHPMs, and the present reaction protocol being readily compliant with parallel synthetic methods (reactant concentration: **1**, **2**, **3** = 5 mmol, 6 mmol, 5 mmol).

In both of these reactions, only one diastereomer of **4**, **4a**, i.e., the *cis*-isomer, was formed with high diastereoselectivity through the generation of three consecutive chiral centers. Replacing urea with the thiourea gave hexahydrothiopyrimidinones. However, the *p*-TSA-catalyzed reaction gave a yield of product **4a** higher than that of the L-proline-catalyzed reaction. **TS-1** was often used in the Biginelli-type reaction of *N*-acyliminium ion and **3**. On the basis of the mechanism shown by Zhu et al.[24] and Overman and Wolfe,[27] the conceivable mechanism for the above two acid-catalyzed reactions is described in Figure 5. According to this, in the presence of acid, firstly *N*-acyliminium ion intermediate **I** was attained by treating urea/thiourea **2** and aldehyde **1**. Now, due to hydrogen bonding, **I** generated a complex with L-proline or

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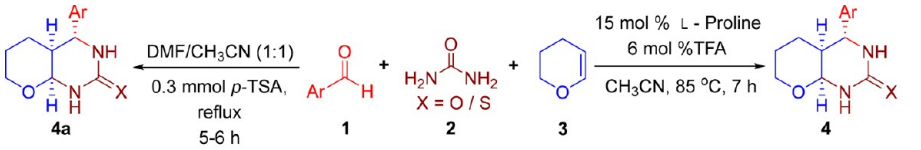
Scheme 1. L-Proline and *p*-TSA-Catalyzed Synthesis of 4 and 4a



Product 4: X = O, Yield = 79-90 % ,Total Entry = 10; X = S, Yield = 78-87 %, Total Entry = 9;
Ar = C_6H_5-, 4-Cl-C_6H_4-, 4-F-C_6H_4-, 4-Br-C_6H_4-, 4-NO_2-C_6H_4-, 3,4-di-(OMe)-C_6H_3-, 2-Cl-C_6H_4, 3,4,5-tri-(MeO)-C_6H_2-, 3-NO_2-C_6H_4-, 2-NO_2-C_6H_4-, 4-C_6H_5-CH_2O-C_6H_4-;
(**1** = 1 equiv, **2** = 1.5 equiv, **3** = 1 equiv)

Product 4a: X = O, Yield = 91-98 %, Total Entry = 8; X = S, Yield = 84-88 %, Total Entry = 4;
Ar = 4-Me-C_6H_4-, 3,4,5-tri-(OMe)-C_6H_2-, 4,5-di-(OMe)-2-(NO_2)-C_6H_2-, 4-(OMe)-C_6H_4-, 4-Br-C_6H_4-, 4-F-C_6H_4-, 2,3-di-Cl-C_6H_4-, 3-(OH)-C_6H_4-, Furan-2-yl-
(**1** = 5 mmol, **2** = 6 mmol, **3** = 5 mmol)

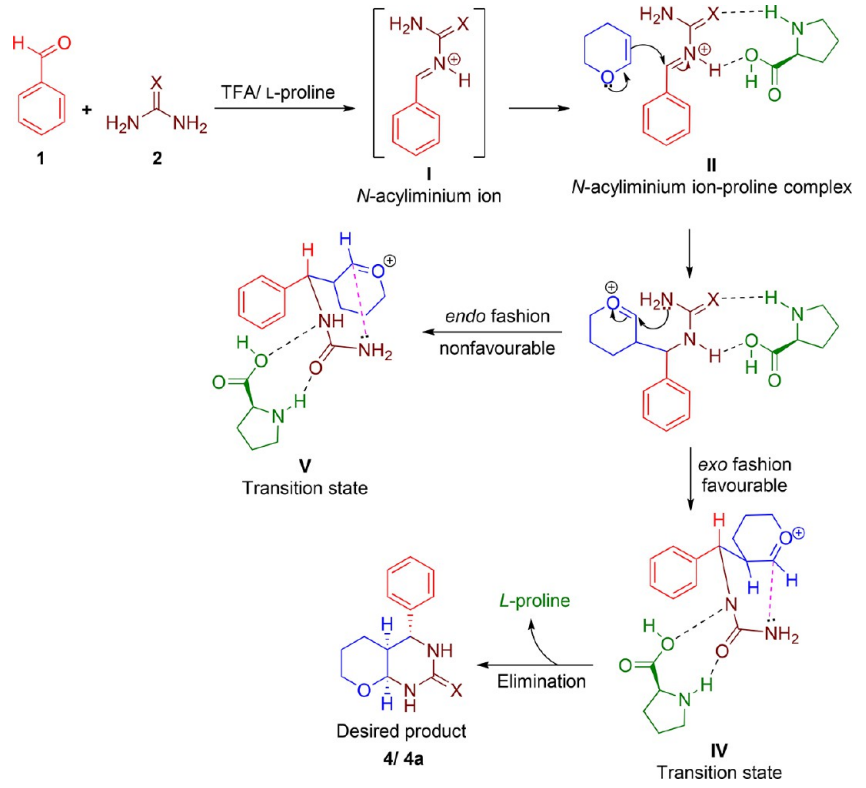


Figure 5. Possible mechanism to synthesize **4**/**4a**.

Scheme 2. TMSCl-Catalyzed Cycloaddition-Based Synthesis of 4b

Product 4b: X = O, Yield = 79-92 %, Total Entry = 4; X = S, Yield = 80-90 %, Total Entry = 7;
R = 4-Me-, H-, 4-(OMe)-, 4-Cl-, 2-F-, 4-F-, 2-(OMe)-, 3-(NO_2)-
(**1** = 5 mmol, **2** = 6 mmol, **3** = 5 mmol)

acid to give intermediate **II**, which was then nucleophilically attacked by 3,4-dihydro-2*H*-pyran to give intermediate **III**. Intermediate **III** then underwent cyclization in two ways, i.e., in *exo* or *endo* manner, to form transition states **IV** and **V**. The negligible severe steric interaction between the 2,3,4,5-tetrahydropyrylium ring and the ureidyl or thioureidyl moiety in the *exo* transition **IV** compared to the *endo* **V** led to formation of the final product **4**/**4a** (**TS-1**).

Zhu et al.[24] designed the diastereoselective synthesis of **4b** by the treatment of **1** (5 mmol) with **2** (6 mmol) to afford the intermediate *N*-acyliminium ion **I**, which then undergoes a hetero-Diels–Alder/[4+2]-cycloaddition reaction with **3** (5 mmol) in the presence of 5 mmol TMSCl in CH_3CN/DMF

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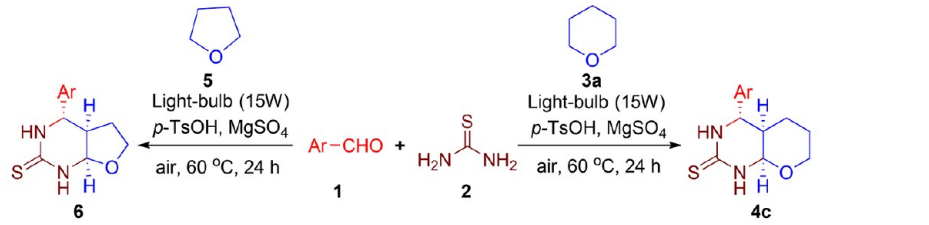
Scheme 3. Synthesis of 4c and 6 with *p*-TSA Using Visible Light Irradiation



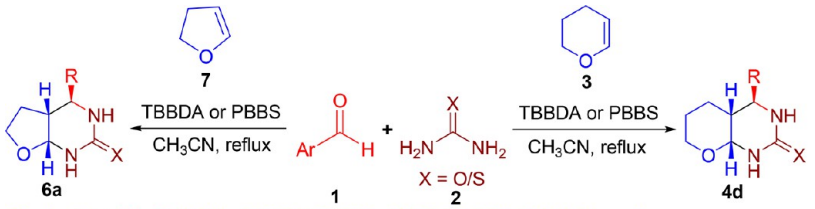
Product 4c: Yield = 48-69%; Total Entry = 12; **Product 6:** Yield = 42-64 %, Total Entry = 8;
Ar = 4-(OMe)-C_6H_4-, 4-Me-C_6H_4-, 4-iPr-C_6H_4-, 4-Cl-C_6H_4-, 3-Cl-C_6H_4-, 2-Cl-C_6H_4-, 2-(OMe)-C_6H_4-, Thiophene-2-yl-, C_6H_5-, 4-^{t}Bu-C_6H_4-, 3-F-C_6H_4-, Furan-2-yl-
(**1** = 5 mmol, **2** = 7.5 mmol, **3a** = 10 mL, *p*-TsOH = 1 mmol, $MgSO_4$ = 5 mmol)

N, *N*, *N*′, *N*′-tetrabromobenzene-1,3-disulfonamide (**TBBDA**)

Poly(*N*-bromo-*N*-ethyl-benzene-1,3-disulfonamide (**PBBS**)

Figure 6. Structure of TBBDA and PBBS.

Scheme 4. TBBDS/PBBS promoted synthesis of 4d and 5a



Product 4d: X = O, Yield = TBBDA 82-95%, PBBS :79-90%; Total Entry = 4;
X = S, Yield = TBBDA 82-89 %, PBBS = 79-81 %, Total Entry =3;
R = 4-Cl-C_6H_4-, 4-bi-C_6H_4-, Naphthalene-2-yl-, 4-NO_2-C_6H_4-
Product 6a: X= O, Yield = TBBDA 91-94 %, PBBS = 84-85 %, Total Entry = 3;
X = S, Yield = TBBDA 89-90 %, PBBS = 80-85 %, Total Entry = 3;
R = 4-Me-C_6H_4-, 2-(OH)-3-(OMe)-C_6H_3-, 2-Cl-C_6H_4-
(**1** = 1 mmol, **2** = 1 mmol, **3** = 1 mmol, TBBDA/PBBS = 0.18 mmol, CH_3CN = 5 mL)

(2:1) under reflux (Scheme 2). Three chiral centers were generated in **4b**, which was formed as a major product by the addition of *N*-acyliminium ion intermediate **I** and dienophile **3**, while the product formed by *endo* addition was not observed. The isolated yield of **4a** was not affected by the presence of various substituents on the aromatic ring of **1**. The probable mechanism followed in this approach is similar to that shown in Figure 5.

Guo et al.[28] developed tetrahydropyrimidine thiones (THMPs) **4c** or **6** in excellent yield under visible light irradiation. The method involved 3-CR of diversified aryl aldehydes **1** (5 mmol) with **2** (7.5 mmol) and tetrahydropyran (THP, 10 mL) **3a** or tetrahydrofuran (THF, 10 mL) **5** in the presence of *p*-TsOH (1 mmol) along with 5 mmol $MgSO_4$ as the catalyst at 60 °C (Scheme 3). The electronic nature and position of various substituents on **1** (i.e., ERG/EWG) greatly affected the product formation. **1** bearing ERGs showed better reactivity than electron-withdrawing groups. The reaction is highly stereoselective with a ratio greater than 19:1. The advantage of this method was the use of metal-free conditions. In this method, a lower yield of product was obtained compared to that with other reported methods, and also this protocol takes the longest time for completion compared to the other reported synthesis of **TS-1**. This group has developed a 4-arylhexahydrofuranopyrimidine derivative instead of 4-aryloctahydropyranopyrimidines.

TBBDA and PBBS are effective reagents for many organic transformations (Figure 6). Ghorbani-Vaghei et al.[29] synthesized **4d** and **6a** (Scheme 4) diastereoselectively through the Biginelli-type molar equiv reaction of **1** with **2** and cyclic enol ethers, 2,3-dihydrofuran **3** and **7** in the presence of PBBS and TBBDA catalyst, and acetonitrile as a solvent under reflux. Often using an aqueous 48% HBr in a catalytic amount gave a yield (15%) lower than that with TBBDA. They catalyzed reaction heterogeneously and recovered, brominated, and reused it several times. The position of various substituents and their position on **1** are important for this reaction. In the case of products **4d** and **6a**, **1** with either EWGs/ERGs reacted successfully and gave a higher yield. However, in case of **4d**, the EWG reacted at a faster rate than the ERG and thiourea showed reactivity lower than that of urea due to the hindered reagent's activity of sulfur as it possessed stronger coordinating ability. In case of **6a**, **1** bearing a nitro group led to the formation of a diastereomeric mixture. Compared to the *p*-TSA-catalyzed reaction using visible light irradiation, use of the present protocol gave a higher yield of 4-arylhexahydrofuropyrimidine and 4-aryloctahydropyranopyrimidine derivatives.

For this TBBDA/PBBS-catalyzed reaction, the probable reaction mechanism is similar, as shown in Figure 7. Initially, carbonyl oxygen of an aldehyde **1** was activated by the catalyst TBBDA to afford **I** on which urea/thiourea **2** attacked to form intermediate **II**. Now, the removal of hypobromous acid

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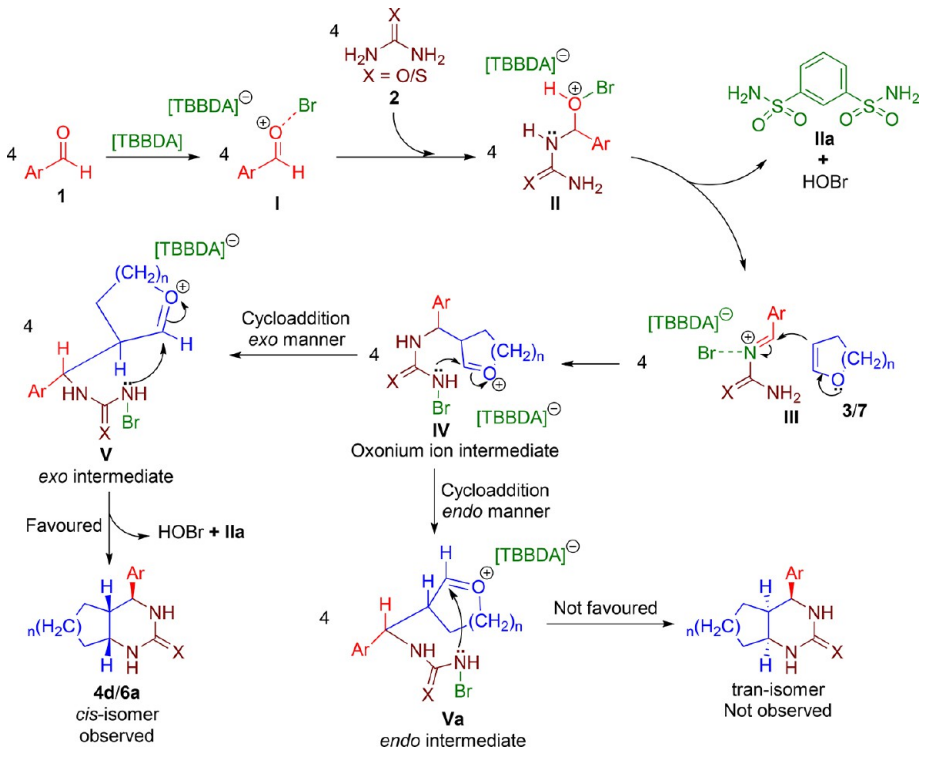
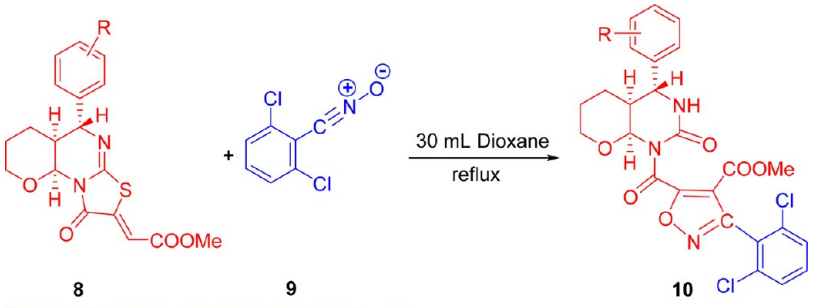


Figure 7. Proposed mechanism to synthesize **4d** and **6a**.

Scheme 5. Synthesis of 10 in Dioxane



(HOBr) and **IIa** gave the intermediate **III**. Now, this intermediate **III** reacted with cyclic enol ether **3**/**7** to form the oxonium ion intermediate **IV**, which then underwent cycloaddition either in *exo*/*endo* fashion to afford the *exo* intermediate **V** and *endo* intermediate **Va**. The intermediate formed by an *exo* attack and that on removal of **IIa** and HOBr gave the corresponding **4d** or **6a**.

2.2. Green-Solvent-Promoted Synthesis of TS-1. Zeng et al.[30] synthesized novel derivatives of 4-aryloctahydropyrano-[2,3-*d*]-pyrimidines **10** via domino 1,3-dipolar cycloaddition or dethionation reaction of methyl[(4*aRS*,5*SR*,10*aRS*)-5-aryl-2-oxo-3,4,4a,10a-tetrahydro-2*H*,5*H*-pyrano[3,2-*e*][1,3]thiazolo-[3,2-*a*]-pyrimidine **8** (1 mmol) with 2,6-dichlorobenzonitrile oxide **9** (2 mmol) in dioxane under reflux for 36 h (Scheme 5). As the reaction was ended, the solvent was evaporated and **10** was purified using column chromatography by taking petroleum ether/ethyl acetate as an eluent. This reaction takes the longest time among all of the reported reaction for **TS-1**.

The probable reported mechanism for **10** is shown in Figure 8. Initially, the 1,3-dipolar cycloaddition reaction between substrates **8** and **9** resulted in the intermediate **I**. Now, **I** gave the corresponding intermediates **II** and **IIa** followed by subsequent ring opening. Finally, in the last step, the sulfur atom was substituted by oxygen in nitrile oxide **9** to afford the targeted **10**.

2.3. Metal Catalyst. Here, antimony trichloride and zirconium(IV) tetrachloride were used as Lewis acid catalysts to afford the TS-1. Bhattacharya et al.[31] explored a mild and efficient diastereoselective reaction between **2** (1.2 mmol), **1** (1 mmol), and cyclic enol ether **3** or **7** (1.5 mmol) to give products **4e** and **6b** with outstanding yield using antimony trichloride in ethanol under reflux (Scheme 6). At room temperature, the reaction proceeded at a very slow reaction rate. Replacement of urea with thiourea did not form the corresponding thio derivative, but a complex mixture was obtained due to the deactivation of the catalyst. Only a single diastereomer was formed with the generation of three

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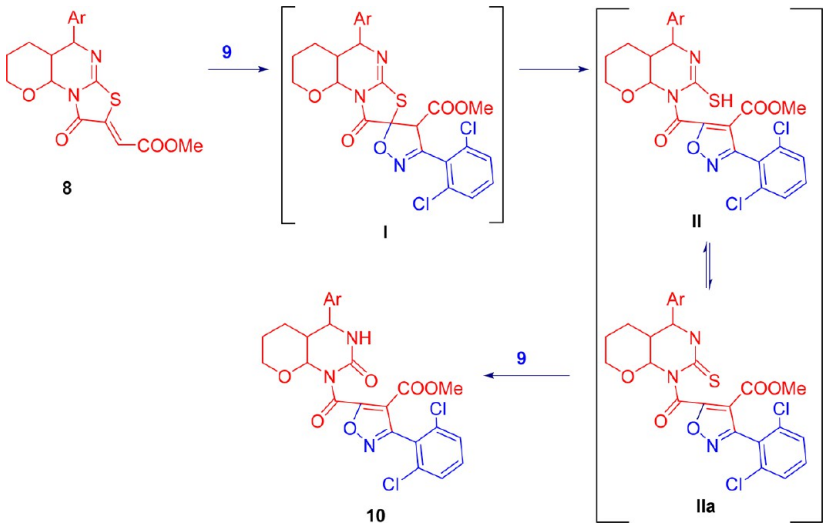
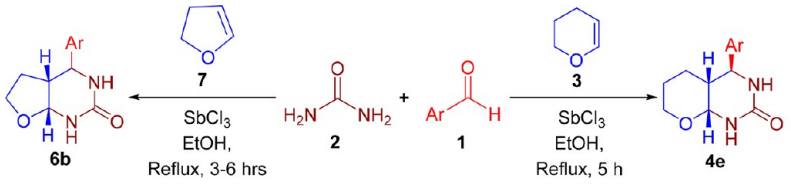


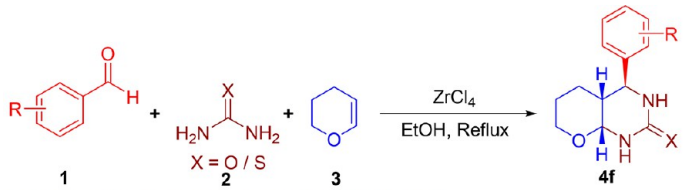
Figure 8. Suggested mechanistic pathways to afford **10** through 1,3-dipolar cycloaddition.

Scheme 6. Synthesizing 6b and 4e Using Lewis Acid Catalyst $SbCl_3$



Product 6b: Yield = 81-93%, Total Entry = 7; **Product 4e** : Yield = 82-94 %, Total Entry = 7;
Ar = C_6H_5-, 4-(NO_2)-C_6H_4-, 4-(OMe)-C_6H_4-, 2-Br-C_6H_4-, 2,6-di-Cl-C_6H_3-, 4-F-C_6H_4-, 2-(NO_2)-C_6H_4-, 4-Me-C_6H_4-, 4-Cl-C_6H_4-, 4-(OH)-3-(OMe)-C_6H_3-, *E*-styryl-
(**1** = 1 mmol, **2** = 1.2 mmol, **3/7** = 1.5 mmol, $SbCl_3$ = 0.1 mmol)

Scheme 7. Utilizing $ZrCl_4$ as a Lewis Acid Catalyst to Afford 22



Product 4f: X = O, Yield = 74-95 %, Total Entry = 12;
X = S, Yield = 75-91 %, Total Entry = 4, Time = 2.4-3 h;
R = H-, 4-Me-, 4-(OMe)-, 4-NO_2-, 3,4,5-tri-(OMe)-, 4-F-, 4-Cl-, 4-Br-, 4-(OH)-, 2-(NO_2)-, 2-Cl-, 3-(NO_2)-
(**1** = 1 mmol, **2** = 1.2 mmol, **3** = 1.5 mmol, $ZrCl_4$ = 10 mol %)

consecutive chiral centers in the product. However, **1** with a nitro group gave a mixture of diastereomers. So, the reaction was very much dependent on the electronic nature of substituents in substrate **1**. The major advantages of this reaction protocol are the use of inexpensive $SbCl_3$ catalyst and ethanol as a nontoxic solvent.

Recently, Pisal et al.[32] synthesized analogues of compound **4**, i.e., **4f**, by using the same substrate scope in ethanol under reflux for 2−3 h as shown in the previous reaction. However, in this case, instead of antimony trichloride they used zirconium tetrachloride as the Lewis acid catalyst (Scheme 7). However, they also used zirconium(II) chloride, but in this case, no product formation occurred. The yield of **4f** was not altered by the presence of either ERGs or EWGs on the aromatic aldehyde **1**. The stereochemistry of product **4f** was identified from its spectroscopic data. This group derived the novel analogues of **4f**, particularly 3,4,5-trimethoxy, 4-bromo, 2-nitro, 2-chloro, and 3-nitro, with a yield higher than that in the previously reported work of Bhattacharya et al.[31] In both of these metal-catalyzed reactions, the product formation was identified by the appearance of red color. This reaction was completed in a shorter reaction time than the previously reported $SbCl_3$-catalyzed reaction.

2.4. Ionic-Liquid (IL)-Catalyzed Synthesis. An ionic liquid is a pure compound as it encompasses ions only with lower viscosity,[33] but actually, it is different from the classical definition of a molten state as discriminated by Seddon.[34] Ionic liquids are liquid at a much lower temperature, i.e., <100 °C, and they have the ability to act as a catalyst due to their chemical and thermal stability, nonflammability, high ionic conductivity, and lower vapor pressure. So, due to this reason, it is considered a substitute for volatile organic solvents in academic laboratories as well as in industry.[35] Here, to synthesize **4g**, Guo et al.[36] used [Hnmp]HSO_4 as a Brønsted

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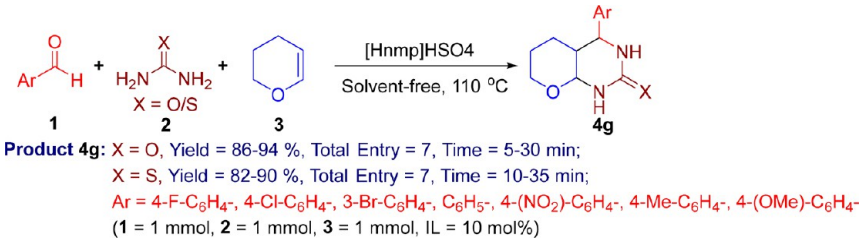
Scheme 8. Use of Ionic Liquid in the Synthesis of 4g



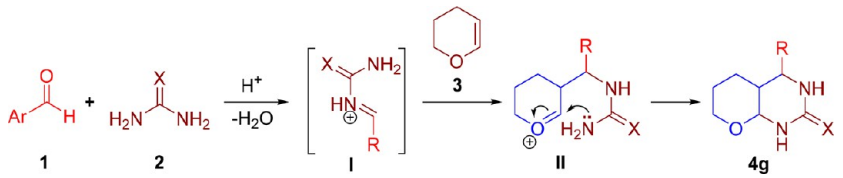


Figure 9. Suggested mechanism for **24**.

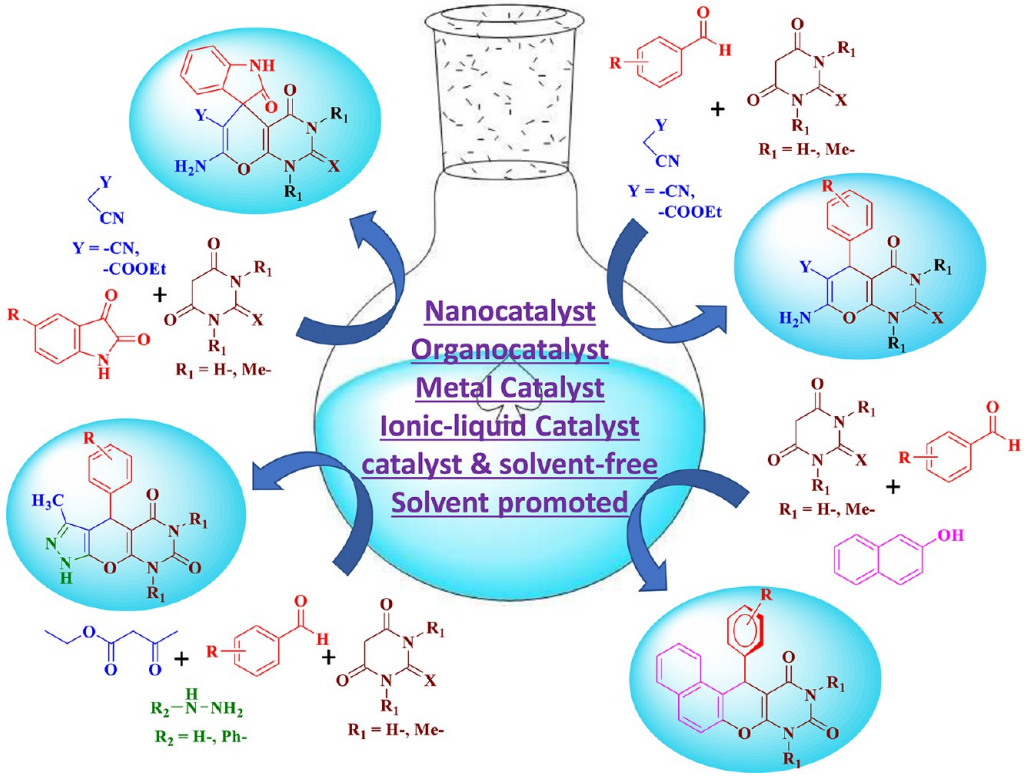


Figure 10. Typical synthetic routes to synthesize diversified pyrano[2,3-*d*]pyrimidindiones/triones by utilizing wide range of catalysts system.

acidic IL (10 mol %) as a catalyst and reported a three-component equimolar treatment of **1**, **2**, and **3** under solvent-free conditions at 110 °C (Scheme 8). The IL used here was recovered easily under reduced pressure followed by drying and reused four times consecutively without loss of its catalytic activity. Pure **4g** was attained using ethanol. **1** bearing ERGs reacted more slowly than those with EWGs.

Among the all of the reported reactions to synthesize **4**−**4g**, the IL-promoted synthesis required the shortest time and solvent-free conditions and gave a higher yield of product. The requirement of higher temperature is one of the disadvantages. So, there is still an opportunity to develop **TS-1** and its analogues using different greener routes. To derive the desired product **4g** using IL as the catalyst, the mechanistic route is described in Figure 9, in which first the transition state **I** was formed by the treatment of **1** with **2** using an acidic IL, which was then treated with **3** to form the intermediate **II**. Now, this intermediate **II** on cyclization gave **4g**.

3. SYNTHESIS OF 5-ARYL-SUBSTITUTED PYRANO[2,3-*d*]PYRIMIDINDIONE/THIONE (TRIONE) DERIVATIVES

Typical synthetic routes to synthesize diversified pyrano[2,3-*d*]pyrimidinediones/triones by utilizing wide range of catalysts system Figure 10.

3.1. Nanocatalyst-Based Synthesis. There are two main categories of catalysts that are used in organic synthesis: homogeneous and heterogeneous catalysts. Homogeneous

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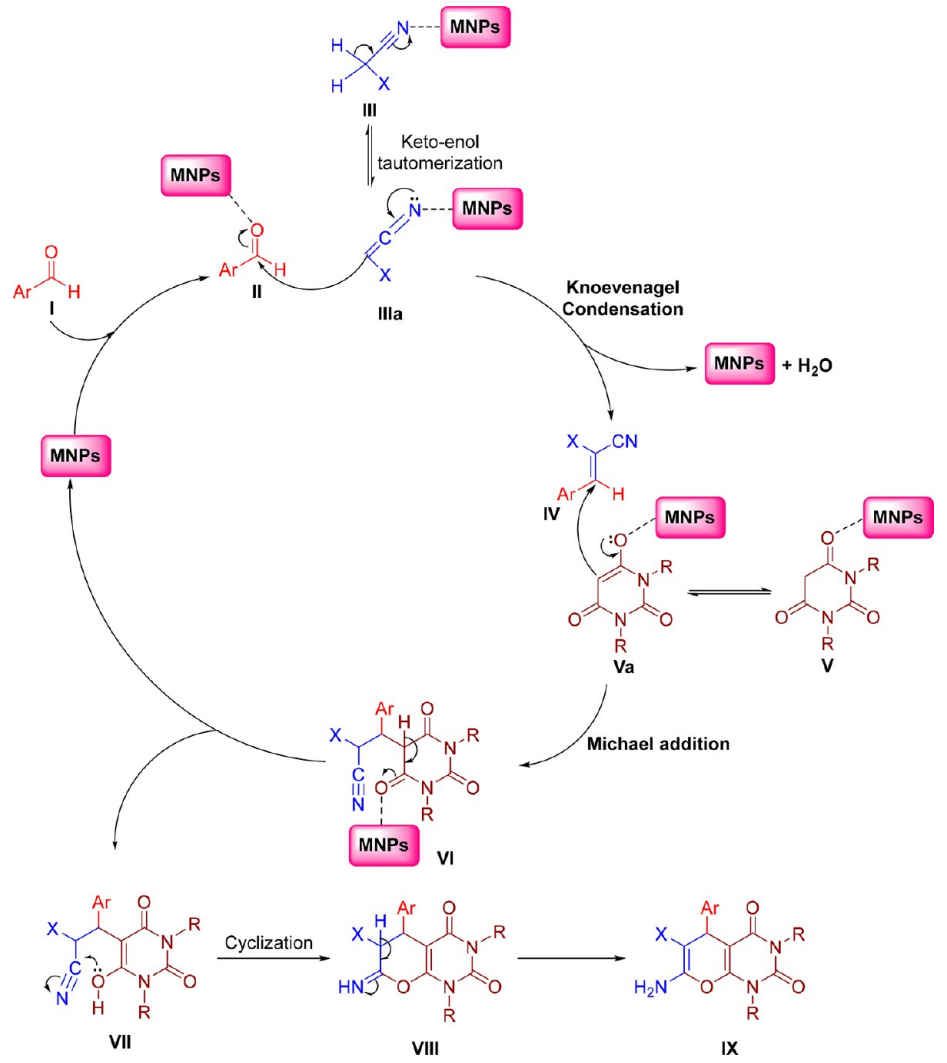

Figure 11. Suggested mechanistic pathways to afford **TS-2** using different nanocatalysts.

catalysts are those in which reactant and catalyst possess the same phase, and heterogeneous catalysts are those in which the catalyst is on the surface where the reaction occurs. Both have their own merits and demerits, i.e., an easy separation in the case of heterogeneous catalyst. Due to their limited surface area, they restrict the reaction rate, while higher reactivity in the case of homogeneous catalyst is difficult to remove from the reaction mixture due to their miscibility in the reaction media, and it is the major problem for its reuse. Therefore, nanoparticles (NPs) are achieved as the bridge between homogeneous and heterogeneous catalysts.[37]

Smaller size, large surface area, higher selectivity and activity, excellent stability and separability, energy efficiency, and atom economy of supported magnetic nanoparticles encourage chemists in academia and industry to utilize it as a catalyst in organic metamorphosis. An effective nanoparticle has a particle size of 1−100 nm and is synthesized using various techniques which involve top-down and bottom-up technologies.[38,39] The top-down method includes spontaneous chemisorption, mechanical grinding, metal vapor, and thermal and chemical breakdown, and the bottom-up method includes sol−gel, electrochemical, sonochemistry, precipitation, microemulsion, solvothermal processing, microwave irradiation, chemical reduction of salts, and template-directed approaches. The various supported nanocatalysts were used to afford the novel 5-aryl-substituted 2*H*-pyrano[2,3-*d*]pyrimidindione (triones) (**TS-2**), and its discrete analogues involved the use of metals like iron, zinc, nickel, silica, titanium, zirconium, and yttrium and uses organic material and their mixed metals in combination with chromium, cadmium, manganese, some lanthanides, and supported NPs.

The common possible mechanism for synthesis of **TS-2** is shown in Figure 11, in which the carbonyl oxygen of an aromatic aldehyde **I** is activated by the nanocatalyst to give intermediate **II**. The nanocatalyst also activated an active methylene group containing **III** to obtain an activated complex **IIIa**. Now, the carbonyl carbon of intermediate **II** is nucleophilically attacked by **IIIa** to give intermediate **IV** through Knoevenagel condensation. The Michael addition of activated barbituric acid derivatives **Va** to **IV** afforded the next intermediate **VI**. After intermediate **VI** was obtained, the magnetic NPs were recovered and **VII** was obtained. Then the cyclization of **VII** gave intermediate **VIII**. Intermediate **VIII** then gave the desired product **IX** through keto−enol tautomerization.

3.1.1. Iron-Based NP-Catalyzed Synthesis. Maleki et al.[40] reported a highly efficient, eco-friendly, and heterogeneous Fe_3O_4-@poly(vinyl alcohol) NP-catalyzed one-pot procedure

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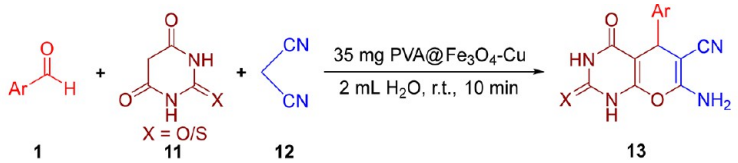
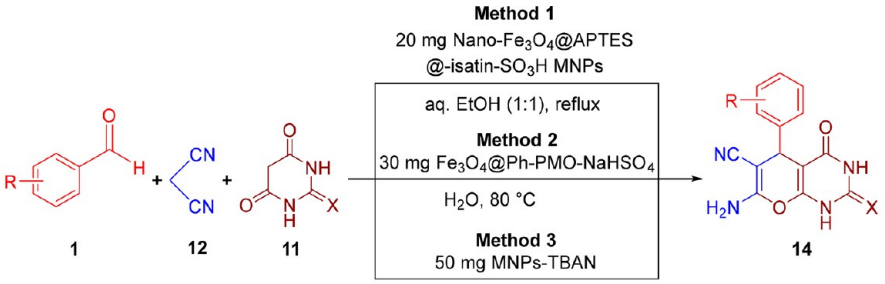
Scheme 9. Synthesis of 13 and Their Analogues Using Fe_3O_4@Poly(vinyl alcohol) NPs



Product 13: X = O, Yield = 80-97%, Total Entry = 15; X = S, Yield = 93-94%, Total Entry = 2,
Ar = C_6H_5-, 4-Br-C_6H_4-, 4-Cl-C_6H_4-, 3-(NO_2)-C_6H_4-, 2-(NO_2)-C_6H_4-, 2,4-di-Cl-C_6H_3-, 4-OH-C_6H_4-, 4-(OMe)-C_6H_4-, 3-OH-C_6H_4-, 2-Br-C_6H_4-, 4-F-C_6H_4-, 2-OH-C_6H_4-, 4-(NMe_2)-C_6H_4-, Thiophene-2-yl-, Pyrrole-2-yl-
(**1** = 1 mmol, **11** = 1 mmol, **12** = 1 mmol)

Scheme 10. Nano-Fe_3O_4@APTES@Isatin-SO_3H-Promoted Synthesis of 14



Product 14: **Method 1**, X = O, Yield = 86-95 %, Total Entry = 18, Time = 7-25 min;
Method 2, X = O, Yield = 80-95 %, Total Entry = 9, Time = 4-40 min,
X = S, Yield = 83-90 %, Total Entry = 5, Time = 30-42 min;
Method 3, X = O, Yield = 87-95 %, Total Entry = 15, Time = 10-25 min,
X = S, Yield = 90-93 %, Total Entry = 7, Time = 15-30 min;
R = H-, 4-Cl-, 4-Br-, 4-(NO_2)-, 2-(NO_2)-, 3-Cl-, 2-Cl-, 4-F-, 3-(NO_2)-, 4-(CHO)-, 2,4-di-Cl-, 2,6-di-Cl-, 4-Me-, 3-Me-, 4-(OMe)-, 3-(OMe)-, 4-(CN)-, 4-Br-, 3-(OH)-, 4-(OH)-, 4-(OPh)-,
(**1** = 1 mmol, **12** = 1 mmol, **11** = 1 mmol)

Table 1. Various Reaction Conditions for Iron-Based MNPs Catalyzed for Production of Derivatives of 15

entry	reaction condition (catalyst, solvent, temperature)	yield (%)	reaction time	reusability of the catalyst	ref
1	10 mol % of nano-Fe_3O_4, EtOH, 40 °C	65−97	22 min		Kidwai et al.[45]
2	5 mol % of $ZnFe_2O_4$ NPs, solvent-free, 75 °C	86−97	7−30 min		Khazaei et al.[44]
3	10 mg of γ-Fe_2O_3@HAp-Ni^{2+} NPs, EtOH, RT	85−95	15−35 min	6	Rezayati et al.[46]
4	20 mol % of Fe_3O_4/Py, EtOH, 25 °C	90−96	60 min	5	Veisi et al.[47]
5	Fe_3O_4@SiO_2@$(CH_2)_3$-urea-SO_3H/HCl MNPs (100 mg), solvent-free, 60 °C	90−98	15−60 min	7	Zolfigol et al.[48]
6	Fe_3O_4@SiO_2-FSA (20 mg), H_2O, 50 °C	73−90	6 h	5	Heydari et al.[49]
7	Fe_3O_4@MCM-41@Zr-piperazine-MNPs (30 mg), aq EtOH (1:1), 80 °C	70−85	10 min	5	Shirini et al.[50]
9	[Fe_3O_4@SiO_2@$(CH_2)_3$-1-methylimidazole]HSO_4 (15 mg), EtOH, reflux	88−95	10−30 min	5	Sajjadifar et al.[51]
10	Fe_3O_4@MCM-41@IL/Pd (1 mg), solvent-free, 40 °C	88−96	10 min	11	Elhamifar et al.[52]
11	γ-Fe_2O_3@[bis-APTES]Cl_2 NPs (15 mg), water−EtOH (1:1), 80 °C	85−97	6−19 min	7	Shirini et al.[53]

to synthesize pyrano[2,3-*d*]-pyrimidinedione **13** by 3-CR of distinctly substituted aryl aldehyde **1** (1 mmol), barbituric acid **11** (1 mmol), and malononitrile **12** (1 mmol) having an active methylene group (Scheme 9). Here, in this heterogeneous catalyst, Cu^{2+} forms a chelated complex with an oxygen atom of barbituric acid and the nitrogen atom of malononitrile and can be reused up to four times consecutively without loss of its activity. In the absence of catalyst, the reaction took place at room temperature, which gave the partial product only. Aryl aldehydes **1** containing various substituents did not significantly alter the yield of product **13**. But when the aromatic ring was changed with thiophene and pyrrole ring, the yield of **13** decreased slightly. The nanocatalyst used here was prepared using an in situ method. The process was initiated under the atmosphere of nitrogen gas in which 72000-MW PVA and distilled water were mixed together with continuous stirring to get the homogeneous mixture. Now, the *p*H of the mixture was made to be 12 via addition of ammonia solution. Then the aqueous solutions of $FeCl_2{\cdot}4H_2O$ and $FeCl_3{\cdot}6H_2O$ were added dropwise to this mixture. Then it was repeatedly stirred for 2 h at room temperature to afford the dark magnetic nanoparticles (MNPs) which were then washed and dried at 70 °C under a vacuum. Then, finally, the mixture of Fe_3O_4@PVA NPs was achieved by addition of Cu(II)$(OAc)_2$ solution. It was further stirred at room temperature for 2 h and then washed and dried.

Sajjadifar and Gheisarzadeh[41] used a heterogeneous aminopropyl-modified magnetic NP coated by isatin-SO_3H, i.e., Fe_3O_4@APTES@isatin-SO_3H, as catalyst. To prepare the

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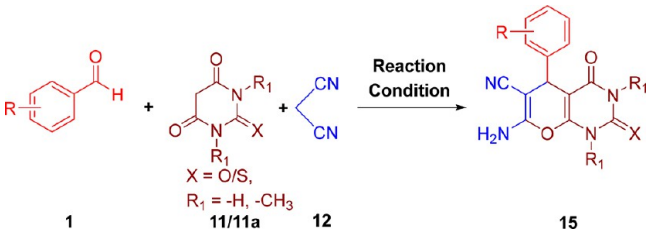
diversified derivatives of **14**, they carried out the treatment of substituted **1** (1 mmol) with **12** (1 mmol) and **11** (1 mmol) in a (1:1) water−ethanol as a solvent under reflux (Method 1, Scheme 10). At the end, the catalyst was separated from the mixture with the help of a magnet and reused without any significant loss of its efficiency up to seven times. The solid residue of product **14** was recrystallized using hot ethanol. Similarly, Haghighat et al.[42] (Method 2, Scheme 10) and Khalili et al.[43] (Method 3, Scheme 10) also reported the synthesis of **14** using the same substrate scope in the presence of a core of phenylene-bridged periodic mesoporous organosilica MNPs immobilized with $NaHSO_4$ (i.e., acidic Fe_3O_4@Ph-PMO-$NaHSO_4$) and bis(4-(dimethylamino)anilino)-triazine-grafted on silica-coated MNPs with a hybrid nanostructure as the catalyst in water at 80 °C and solvent-free conditions at 100 °C. Fe_3O_4@Ph-PMO-$NaHSO_4$ was the heterogeneous catalyst, reused up to five runs, and was a magnetically separable solid acid in which $NaHSO_4$ adsorbed on Fe_3O_4 NPs was coated with a thin layer of Ph-PMO. However, in these three reactions, the electronic nature and position of various EWG/ERG substituents on an aryl aldehyde did not affect the isolated yield of product **14**.

In these three methods, Method 1 gave higher yield in shorted reaction time. The highly efficient and heterogeneous acid−base $ZnFe_2O_4$-catalyzed single-pot 3-CR reported by Khazaei et al.[44] was used to obtain novel analogues of **15** using **1** (1 mmol), **11**/**11a** (1 mmol), and **12** (1.2 mmol) under solvent-free conditions (Table 1, entry 1) (Scheme 11). The

Scheme 11. Reaction Protocol to Synthesize Analogues of 15 Using Different Iron-Based NP Catalysts



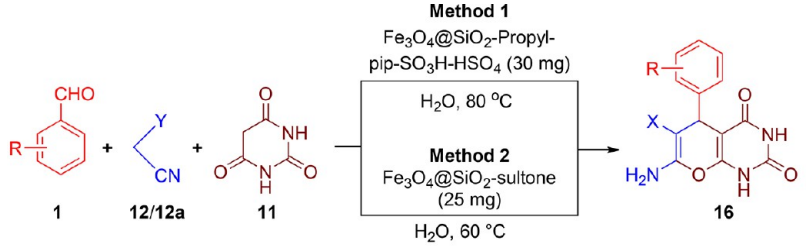
heterogeneous promoter (5 mol %) used here could possess a dual nature, i.e., Lewis acidic nature with Fe^{3+} of Fe_3O_3 and basic nature by O^{2-} of ZnO. Cheap, easy separation, high surface area, the insolubility of the catalyst in solvent, simplicity, high yield, and time efficiency are some of the major merits of this protocol.

Some other groups have also synthesized the novel analogue of **15** using different iron-based nanocatalyst in different solvents and temperatures using the same substrate scope, as shown in Scheme 11 and in Table 1, entries 1−11 (equimolar reactant).

Table 1 shows various reaction conditions for the production of derivatives of **15** from aryl aldehyde **1**, barbituric acid (thiobarbituric acid)/1,3-dimethyl barbituric acid **11**/**11a**, and malononitrile **12**. For all of the entries in Table 1, the reactant concentrations were equimolar (1 mmol) except for **1** (1 mmol), **12** (1.2 mmol), and **11** (1 mmol) and also only for entry 1, where X = O/S, and in all other entries when X = O. Herein different iron-based MNPs as catalysts such as nano-Fe_3O_4, $ZnFe_2O_4$ NPs, γ-Fe_2O_3@HAp-Ni^{2+} NPs, Fe_3O_4/Py, Fe_3O_4@SiO_2@$(CH_2)_3$-urea-SO_3H/HCl MNPs, Fe_3O_4@SiO_2-FSA, Fe_3O_4@MCM-41@Zr-piperazine MNPs, [Fe_3O_4@SiO_2@$(CH_2)_3$-1-methylimidazole]HSO_4, Fe_3O_4@MCM-41@IL/Pd, and γ-Fe_2O_3@[Bis-APTES]Cl_2 NPs were reported here to synthesize the scaffold **15** using different solvent media and temperature (entries 1−11, Table 1). Shirini et al.[50] took the molar ratio of reactants in the order of 1:1.2:1 mmol of **1**, **12**, and **11**, respectively (entry 7). From Table 1, it is observed that the highest isolated yield of **15** was obtained in the case of entries 4 and 5. Among the various MNPs, γ-Fe_3O_4@MCM-41@IL/Pd was reused a maximum of 11 times, providing a higher yield of 88−96% in a shorter reaction time. The Fe_3O_4@SiO_2-FSA-catalyzed reaction takes the longest time to complete compared to all of the other reported methods, as shown in Table 1 (entries 1−11). In all of these reactions, the nanocatalyst could be recovered using an external magnet and reused for several times without any significant loss of its catalytic activity. Kidwai et al.[45] reported that the nano@-Fe_3O_4-promoted reaction gave a yield slightly lower compared to that of others. In all of these reactions, the presence of various EWGs/ERGs did not significantly alter the isolated yield of product **15**.

Rezvani et al.[54] efficiently afforded **16** via reaction of **1** (1 mmol), **11** (1 mmol), and **12**/**12a** (1 mmol) in the presence of heterogeneous silica-coated magnetite-Fe_3O_4 NPs modified by 4-(4-propylpiperazine-1-yl)butane-1-sulfonic acid catalyst in water as greener solvent at 60 °C (Scheme 12). The catalyst was recovered and used again six runs. However, the reaction with ethyl cyanoacetate requires a larger time. In continuation, Pourghasemi-Lati and co-workers[55] reported the synthesis of

Scheme 12. Silica-Coated Magnetic Iron Oxide Catalyzed Synthesis of 16



Product 16: Method 1, Y = -CN, Yield = 87-97 %, Total Entry = 9, Time = 15-30 min,
Y = -COOEt, Yield = 50-90 %, Total Entry = 6, Time = 50-90 min;
Method 2, Y = -CN, Yield = 90-98 %, Total Entry = 12, Time = 10-35 min,
Y = -COOEt, Yield = 50-90 %, Total Entry = 5, Time = 25-50 min;
R = H-, 4-Cl-, 4-(NO_2)-, 3-(NO_2)-, 4-(OMe)-, 4-Me-, 2-Cl-, 4-Br-, 4-(OH)-, 4-(CHO)-, 2-(NO_2)-, 4-(OH)-, 3-(OMe)- (**1** = 1 mmol, **12**/ **12a** = 1 mmol, **11** = 1 mmol)

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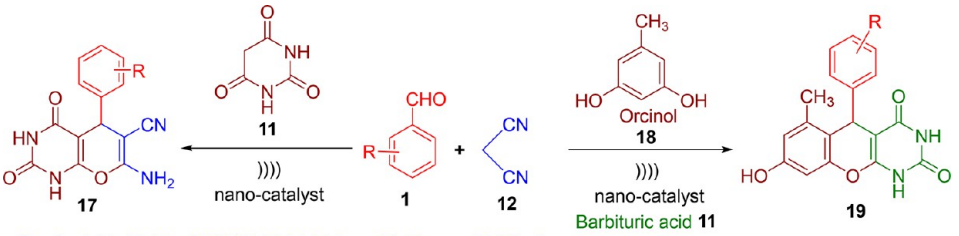
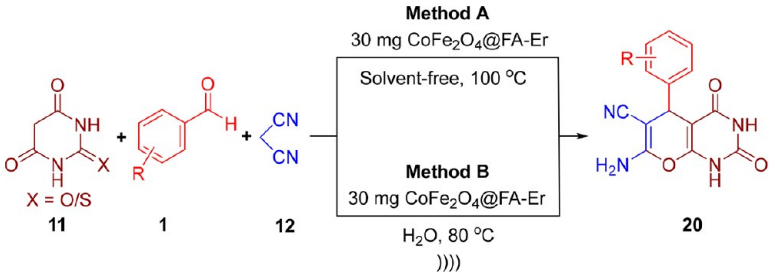
Scheme 13. Synthesis of 17 and 19 Using Fe_3O_4@SiO_2@BenzIm-Fc[Cl]/$ZnCl_2$ NPs



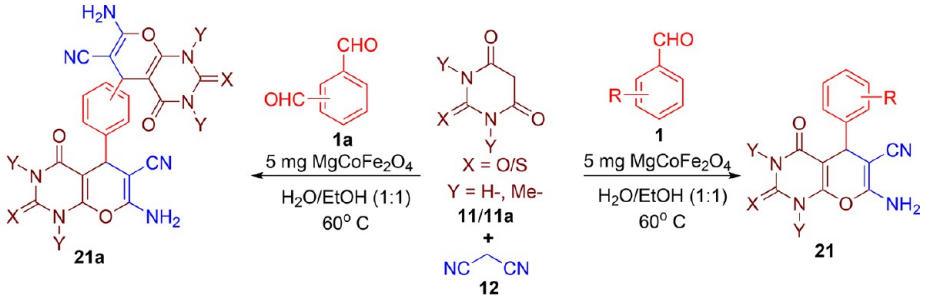
Product 17: Yield = 87-98 %, Total Entry = 10, Time = 10-15 min;
Product 19: Yield = 85-95 %, Total Entry = 12, Time = 20-25 min;
R = 4-Me-, H-, 4-Cl-, 4-^{i}Pr-, 3-(NO_2)-, 2-Br-, 4-Br-, 4-F-, 4-(OMe)-, 4-(NO_2)-, 3-Cl-, 2-Cl-
(**1** = 1 mmol, **12** = 1.1 mmol, **11** = 1 mmol, **18** = 1 mmol, nano-catalysts = 8 mg)

Scheme 14. Utilizing the Heterogeneous Catalyst $CoFe_2O_4$@FA-Er to Afford 20



Product 20: Method A, Yield = 87-96 %, Total Entry = 12, Time = 15-30 min;
Method B, Yield = 87-94 %, Total Entry = 12, Time 8-15 min;
R = 3-(NO_2)-, 4-(NO_2)-, 4-(OMe)-, 4-Br-, 4-Cl-, 4-(OH)-, 2,3-di-Cl-, 4-Cl-3-(NO_2)-, 2-F-
(**1** = 1 mmol, **2** = 1 mmol, **3** = 1 mmol)

Scheme 15. Synthesizing 21 and Its analogue 21a Using $MgCoFe_2O_4$ MNPs



Product 21: X = O, Y = -H, Total Entry = 4, Yield = 89-93%; R = 3-Br-, 3-Cl-, 2-(OMe)-, 3-CH_3-;
X = S, Y = -H, Total Entry = 1, Yield = 90%; R = 3-(NO_2)-;
X = O, Y = -CH_3, Total Entry = 11, Yield = 87-98%; (**1** = 1 mmol, **12** = 1 mmol, **11/11a** = 1 mmol)
R = -H, 2-Cl-, 2,6-diCl-, 4-Cl-, 2-F-, 3-(OMe)-, 4-(OMe)-, 2-CH_3-, 4-CH_3-, 2-(NO_2)-, 4-(NO_2)-;
Product 21a: X = O, Y = -H, Total Entry = 2, Yield = 82-85%; R = 3-(CHO)-, 4-(CHO)-;
X = O, Y = -CH_3, Total Entry = 2, Yield = 85-87%, R = 3-(CHO)-, 4-(CHO)-
(**1** = 1 mmol, **12** = 2 mmol, **11** = 2 mmol)

16 using the same substrate scope (equimolar) as shown in Scheme 12. But in this case, they used heterogeneous silica-coated Fe_3O_4 immobilized with a butane-1-sulfonic acid catalyst in water at 60 °C. As the reaction was terminated, the catalyst was recovered and reused several times with a slight change in the efficiency. In both reactions, the nature as well as the position of various substituents on **1** did not showed any senseful effect on extracted product **16**. However, Method 2 gave higher isolated yield of **16** in shorter reaction time than Method 1.

Gholamhosseini-Nazari and co-workers[56] developed environmental friendly supported heterogeneous catalyst Fe_3O_4@SiO_2-BenzIm-Fc[Cl]/$ZnCl_2$ and used it to attain pyran-annulated bis-heterocyclic scaffolds **17** and **19** and their derivatives using an ultrasound-assisted method. They used a three-component equimolar reaction of different aryl aldehydes **1**, **12**, and **11** or orcinol **18** in aqueous ethanol (2:1) as a solvent (Scheme 13). After the end of the treatment, the catalyst was recovered and reused six times simultaneously with no measurable loss in its ability. These nanoparticles have a monodispersity with an average size of 35 nm. In both synthetic pathways, the presence of different ERGs/EWGs on an aromatic ring of **1** did not affect the isolated yield of products **17** and **19**.

Sorkhabi et al.[57] developed the heterogeneous nanostructured erbium coated with folic acid immobilized on cobalt ferrite and utilized it as catalyst to carried out the reaction of **11** (1 mmol) with **1** (1 mmol) and **12** (1 mmol)

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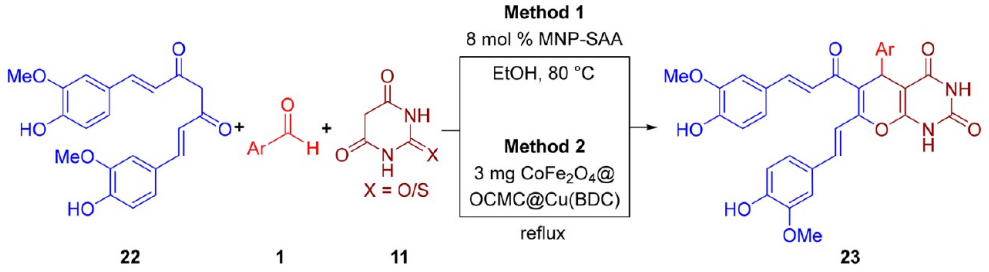
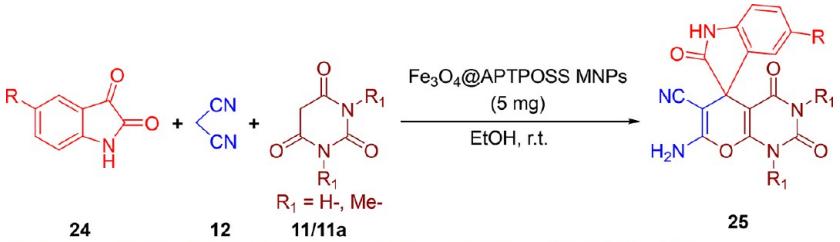
Scheme 16. Synthesizing 23 Using MNP-SAA



Product 23: **Method 1**, X = O, Yield = 75-90 %, Total Entry = 11, TIme = 6-12 h,
X = S, Yield = 85-92 %, Total Entry = 3, Time = 6-10 h;
Method 2, X = O, Yield = 81-94 %, Total Entry = 10, Time = 120-150 min;
Ar = 4-Cl-C_6H_4-, 4-(NO_2)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-Br-C_6H_4-, 2,4-di-Cl-C_6H_3-, 4-(CN)-C_6H_4-, 3-(OH)-C_6H_4, 4-(SCH_3)-C_6H_4-, C_6H_5-, 3-(NH-C_2H_2)-C_6H_4-, 3,4-di-F-C_6H_3-, 2,6-di-Cl-C_6H_3-, 3-indolyl-, 4-F-C_6H_4-, 3-(OH)-4-(OMe)-C_6H_3-, 4-(SMe)-C_6H_4-, Thiophene-2-yl-, Furan-2-yl-
(**22** = 1 mmol, **1** = 1 mmol, **11** = 1 mmol)

Scheme 17. Fe_3O_4@APTPOSS MNP-Promoted Synthesis of 25



Product 25: Yield = 69-83%, Total Entry = 3, Time = 52-55 min; R = H-, Br-, -NO_2
(**24** = 1 mmol, **12** = 1 mmol, **11**/**11a**= 1 mmol)

under sonication in water at 80 °C or in the absence of solvent at 100 °C to get diverse analogues of **20** (Scheme 14). At the end, an external magnet was used to separate the catalyst and reutilized until six times. The remained crude solid was then separated with ethyl acetate which then dried and the solvent was evaporated to attained the crude product which was then recrystallized using hot ethanol. **1** with either ERG/EWG gave higher isolated yield of the **20** in short time.

Atarod et al.[58] reported an eco-friendly three-component reaction protocol to synthesize **21** and their bis-derivatives **21a** by making use of heterogeneous magnesium−cobalt ferrite as a nanocatalyst and H_2O−EtOH by the treatment of **11**/**11a** (1 or 2 mmol), aromatic aldehyde **1**/**1a** (1 mmol), and **12** (1 or 2 mmol) at 60 °C (Scheme 15). However, the reaction also proceeded at room temperature (RT), but the yield got decreased. Here, the electronic nature and position of different substituents on **1**/**1a** did not affect the overall yield of the **21**/**21a**. This recovered catalyst was used for a further six cycles. This nanocatalyst could be synthesized from an aqueous extract of apple skin via the green sol−gel autocombustion technique.

Panahi and co-workers[59] described a protocol for synthesis of curcumin-based derivatives of **23** using the reaction of curcumin **22** (1 mmol) as the main reagent with **1** (1 mmol) and **11** (1 mmol) in the presence of MNPs, Fe_3O_4@SiO_2 (8 mol %) supported sulfanilic acid in ethanol at 80 °C (Scheme 16). These prepared MNPs have an average size of 14 nm. **1** carrying an EWG considerably produced a higher isolated yield of the product **23** than those carrying ERG. However, heteryl aldehydes also gave a high yield. However, the mechanism to synthesize pyranopyrimidine[2,3-*d*]diones using curcumin as an active methylene group containing species was similar to the mechanism as shown in Figure 11. After this, Ghaffarian et al.[60] developed 3 mg of $CoFe_2O_4$@OCMS NPs functionalized by Cu(BDC) as catalyst to afford a novel analogue of **23** using the same substrate scope of **22**, **1**, and **11** in ethanol under reflux at 80 °C (Scheme 16). In comparison with the work of Panahi et al.,[59] here discrete **1** with ERGs/EWGs did not affect the isolated yield of the product **23**, and unsubstituted aromatic aldehydes gave a decreased yield compared to that of the other substituted aromatic aldehydes. The major benefit of this protocol is the decreased reaction time, i.e., 120−150 min, and increased yield of the product. In both reactions, after completion, the catalyst was recovered and reused up to five and six runs without loss of its catalytic activity.

Safaei-Ghomi et al.[61] synthesized analogues of **25** by treating isatin **24** (1 mmol) with malononitrile **12** (1 mmol) and **11**/**11a** (1 mmol) at RT in ethanol using the nanocatalyst (5 mg) Fe_3O_4@APTPOSS MNPs (Scheme 17). At the end, the catalyst was detached from the reaction mixture and reused for the next runs. The precipitates were filtered and dried to attain the pure isolated yield of **25**. In the presence of the catalyst, polyhedral oligomeric silsesquioxane (POSS) with an inorganic core of silicone has a size of nearly 0.45 nm diameter.

Thereafter, Dadaei and Naeimi[62] designed core−shell structured NPs of cobalt-ferrite functionalized by guanidine, i.e., $CoFe_2O_4$@SiO_2-guanidine and was utilized as the catalyst to synthesize derivatives of **25** under the same substrate scope in water using sonication condition of 40 W (Scheme 17). As the reaction was completed, the catalyst was recovered and reused for the next three consecutive runs, and the pure product was attained by washing with water and drying. This reaction was completed in just 8−10 min and increased the

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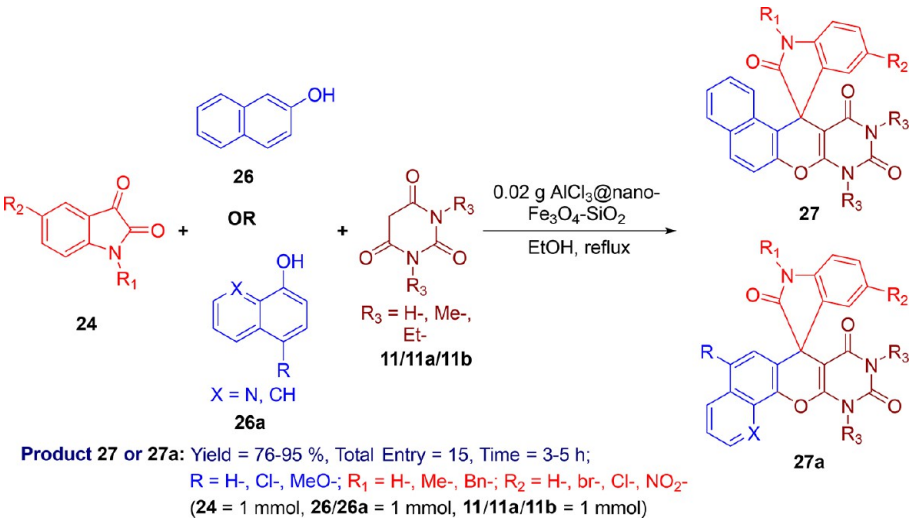
Scheme 18. Synthesizing 27 and 27a by Utilizing $AlCl_3$@Nano-Fe_3O_4-SiO_2



Product 27 or 27a: Yield = 76-95 %, Total Entry = 15, Time = 3-5 h;
R = H-, Cl-, MeO-; R_1 = H-, Me-, Bn-; R_2 = H-, br-, Cl-, NO_2-
(**24** = 1 mmol, **26/26a** = 1 mmol, **11/11a/11b** = 1 mmol)

reaction yield of about 91−92% compared to reaction presented by Safaei-Ghomi et al.[61]

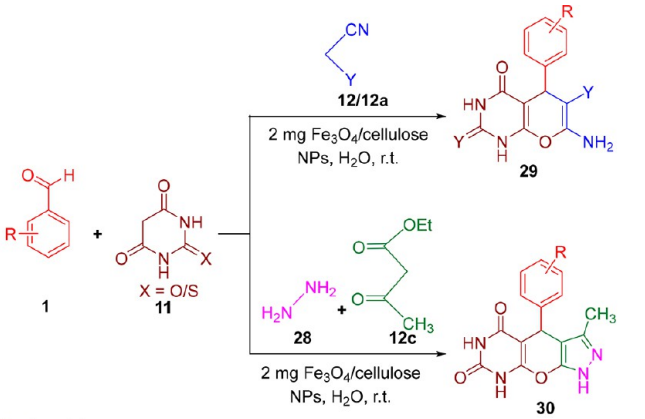
Nikoofar et al.[63] derived a novel core−shell $AlCl_3$@nano-Fe_3O_4-SiO_2 nanocatalyst and synthesized spiro-[benzochromeno[2,3-*d*]pyrimidine-indolines] **27/27a** via equimolar (1 mmol) reaction of isatin **24** derivatives with *β*-naphthol **26/26a** and **11/11a/11b** under reflux in ethanol (Scheme 18). An external magnet was used to separate out the catalyst which was then washed with ethanol to gain the recovered catalyst and used again four times. The pure product of **27/27a** was obtained after evaporation of solvent.

Maleki et al.[64] reported the chemoselective synthesis of analogues of **29** and pyrazolopyrano- pyrimidines **30** via three-component condensation reaction between **1** (1 mmol), **11** (1 mmol), and **12/12a** (1 mmol), and four-component condensation reaction between **1** (1 mmol), **11** (1 mmol), hydrazine **28** (1 mmol), and ethyl acetoacetate **12c** (1 mmol), respectively, via use of the catalytic amount of cellulose-based nanocomposite in water at RT (Scheme 19). A natural organopolymer, cellulose, contains 1,4-anhydrous-D-glucopyranose units. Only one product was formed in this reaction. However, in absence of a catalyst, the reaction took place but only a trace amount of the product was obtained. The electronic nature and position of various substituents on **1** did not appreciably affect the yield of products **29** and **30**, and aryl aldehydes **1** carrying electron-releasing substituents took less time than those carrying EWGs. The most advantageous aspectr of using this protocol was the biodegradability of the nanocatalyst.

Mahmoudi-Gom Yek et al.[65] used a supported heterogeneous N_6-Schiff base complex coated by Cu(II) on the surface of Fe_3O_4-magnetized graphene oxide nanosheets to prepare GO-Fe_3O_4@SPNC-catalyzed one-shot synthesis of tricyclopyranopyrimidine **32** along with its diverse analogues by utilizing a three-component equimolar reaction of **1** with **11a** and 3-cyano-6-hydroxy-4-methylpyridine-2(1*H*)-one **31** under the solvent-free conditions at 70 °C (Scheme 20). The catalyst was reused up to seven times. The presence of various groups on an aromatic ring of **1** did not affect the isolated yield of the **32**.

Soleimani et al.[66] synthesized pyrano[2,3-*d*]-pyrimidine-5-carboxamide **35** using heterogeneous acid catalyst i.e. immobilized ciprofloxacin on surface-modified magnetic silica NPs catalyzed single-pot three-component reaction of

Scheme 19. Synthesizing 29 and 30 via Use of Fe_3O_4/Cellulose NPs at RT



Product 29: X = O, Y = -COOEt, Yield = 90-98%, Total Entry = 5, Time = 20-40 min;
R = H-, 4-Me-, 4-(OMe)-, 4-Cl-, 4-(NO_2)-;
Y = -CN, Yield = 90-98%, Total Entry = 5, Time = 20-35 min;
R = H-, 4-Br-, 2-(NO_2)-, 3-(NO_2)-, 4-(NO_2)-;
X = S, Y = -CN, Yield = 76-96%, Total Entry = 5, Time = 20-40 min;
R = 4-(OMe)-, 4-Br-, 2-(NO_2)-, 3-(NO_2)-, 4-(NO_2)-;
Product 30: Yield = 82-95%, Total Entry = 9, Time = 15-40 min;
R = H-, 4-Me-, 2-Cl-, 4-Cl-, 2-(NO_2)-, 3-(NO_2)-, 4-(NO_2)-, 4-Br-, 2-thienyl-
(**1** = 1 mmol, **11** = 1 mmol, **12/12a** = 1 mmol, **28** = 1 mmol, **12c** = 1 mmol)

salicylaldehyde **33** (1 mmol) along with **11** (1 mmol) and substituted isocyanide **34** (1 mmol) in the water−ethanol at 60 °C (Scheme 21). This heterogeneous nanocatalyst was prepared via sol−gel technique in which magnetic silica NPs were prepared by a coating of magnetic nanoparticles using silica and their surface was modified and functionalized covalently by (3-chloropropyl)triethoxysilane and ciprofloxacin. Then it was separated from the product **35** and used with no significant loss of its efficiency for five times. Compounds with ERGs reacted better than those with EWGs to attain **35**.

Kefayati et al.[67] derived three sulfonic acid grafted catalysts such as Fe_3O_4-SO_3H, Fe_3O_4@SiO_2-SO_3H, and Fe_3O_4@MCM-48-SO_3H as heterogeneous catalysts and the homogeneous catalyst 1-methylimidazolium hydrogen sulfate, i.e., [HMIm]-[HSO_4]. They developed two methods to synthesize tetracyclicpyrano[2,3-*d*]pyrimidinediones **36** in which Method 1 involves the use of a heterogeneous catalyst (50 mg) and

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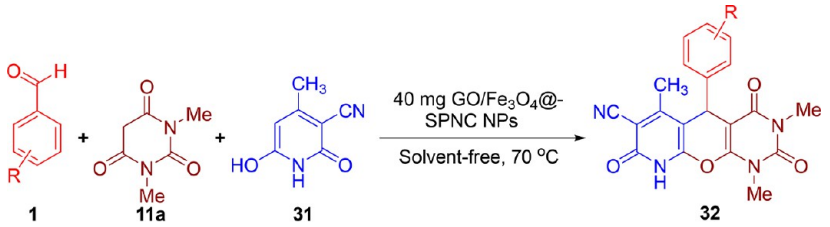
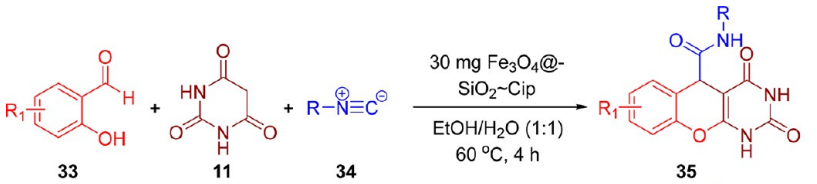
Scheme 20. GO/Fe_3O_4@SPNC-Promoted Synthesis of 32



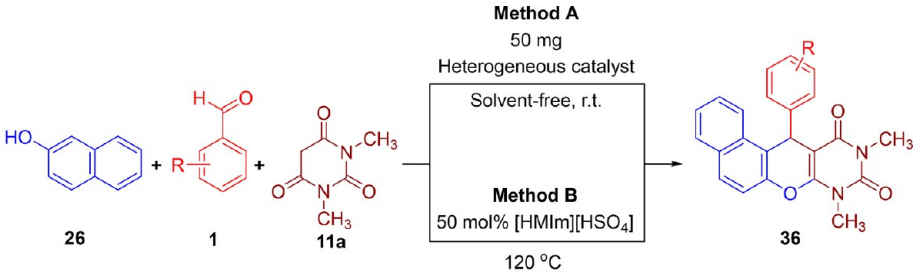
Product 32: Yield = 79-95 %, Total Entry = 10, Time = 10-30 min,
R = H-, 2-(OH)-, 2-(NO_2)-, 4-(NO_2)-, 4-Br-, 3-Br-, 2-Cl-, 4-Cl-, 2,4-di-Cl-, 4-F-
(**1** = 1 mmol, **11a** = 1 mmol, **31** = 1 mmol)

Scheme 21. Synthesizing 35 Utilizing Fe_3O_4@SiO_2-Cip



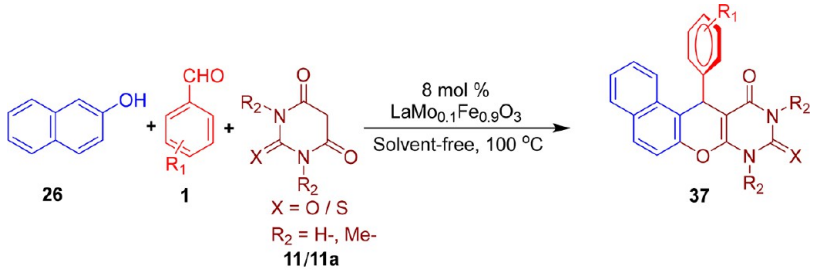
Product 35: Yield = 83-99 %, Total Entry = 8; R_1 = H-, 3-Me-, 5-Br-, 5-(NO_2)-; R = ^{t}Bu-, cyhex-
(**33** = 1 mmol, **11** = 1 mmol, **34** = 1 mmol)

Scheme 22. Synthesizing 36 by Utilizing Two Different Conditions



Product 36: Method A, Yield = 85-98 %, Total Entry = 10, Time = 18-25 min;
Method B, Yield = 75-90 %, Total Entry = 10, Time = 30-60 min;
R = H-, 2-Cl-, 4-Cl-, 4-Br-, 4-Me-, 3-(NO_2)-, 4-(NO_2)-, 2-(OMe)-, 3-(OMe)-, 4-(OMe)-
(**26** = 1 mmol, **1** = 1mmol, **11a** = 1.2 mmol)

Scheme 23. $LaMo_{0.9}O_3$-Promoted Synthesis of 37



Product 37: X = O/S, R_2 = -H, Yield = 89-92 %, Total Entry = 13, Time = 20-40 min;
X = O, R_2 = -Me, Yield = 89-90 %, Total Entry = 4, Time = 84-90 min;
R_1 = H-, 4-(NO_2)-, 3-(NO_2)-, 4-F-, 4-Br-, 3-Br-, 2,4-di-Cl-
(**26** = 1 mmol, **1** = 1 mmol, **11/11a** = 1.2 mmol)

Method 2 involves the use of (50 mol %) homogeneous catalyst. They used reaction of β-naphthol **26** (1 mmol) with aryl aldehyde **1** (1 mmol) and **11a** (1.2 mmol) under solvent-free conditions at RT and at 120 °C, respectively (Scheme 22). In the first method, the mixture was treated with crushed ice, and the crude product was recrystallized using ethanol to get the pure product **36**. However, the catalyst was detached from it with the help of a magnet and used further for five runs. In the second method, the reaction mixture was cooled to RT and then it was diluted with water, and the crude **36** was recrystallized from ethanol. It is observed that **1** with EWGs reacted at a faster rate than those with ERGs. However, the desired product was not formed with aliphatic aldehydes.

Rahmatinejad and Naeimi[68] developed a nontoxic and recyclable perovskite-type crumpled $LaFeO_3$ doped by molybdenum nanosheets as a catalyst which was synthesized

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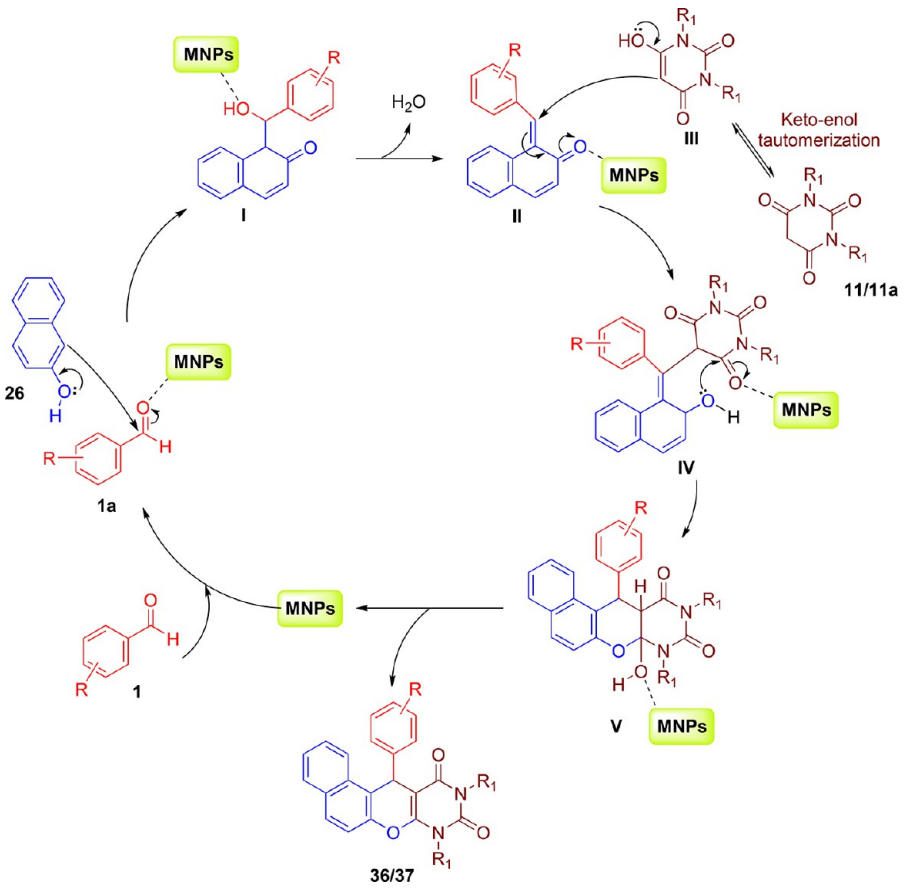
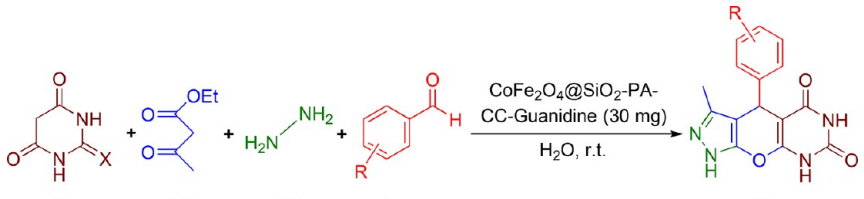


Figure 12. Proposed mechanism for the synthesis of analogues of naphthopyrano[2,3-*d*]pyrimidindione.

Scheme 24. Utilizing $CoFe_2O_4$@SiO_2-PA-CC-Guanidine NP-Catalyzed Synthesis of 38



Product 38: X = O, R_1 = H, Yield = 89-98 %, Total Entry = 7, Time = 15 min;
X = S, R_1 =H-, Yield = 85-93 %, Total Entry = 5, Time = 15 min;
X = O, R_1 = Me-, Yield = 87-96 %, Total Entry = 3, Time = 15 min;
R = H-, 4-Cl-, 4-Me-, 2-Cl-, 4-Br-, 4-(OMe)-, 2-(OMe)-
(**11** = 0.5 mmol, **12c** = 0.5 mmol, **28** = 0.5 mmol, **1** = 0.5 mmol)

using a citric acid-based sol−gel route to provide a one-pot synthesis of naphthopyranopyrimidines **37** via treatment of **26** (1 mmol), various aromatic aldehydes **1** (1 mmol), and **11**/**11a** (1 mmol) without solvent at 100 °C (Scheme 23). After the reaction ended, the catalyst was recovered and reused five times without a considerable efficiency loss. **1** with either EWGs/ERG did not considerably affect the isolated yield of the product **37**.

The probable mechanism that afforded naphthopyrano[2,3-*d*]pyrimidine is shown in the Figure 12. First, MNPs activate the carbonyl oxygen atom of the aryl aldehyde **1** to intermediate **1a** on which the *β*-naphthol **26** attacked nucleophilically to get the intermediate **I**. Removal of a water molecule from it produced *ortho*-quinone methides **II**. Now, Michael addition of **III** (obtained from **11**/**11a** via Keto-enol tautomerization)to the intermediate **II** afforded **IV**. Intermediate **IV** on cyclization gave intermediate **V**. Then the removal of the water molecule gave the desired product naphthopyrano[2,3-*d*]pyrimidinedione **36**/**37**.

Rostami and Shiri[69] utilized $CoFe_2O_4$@SiO_2-PA-CC-guanidine MNPs as heterogeneous catalysts to synthesize **38** through the equimolar reaction of **11**, **12c**, **28**, and **1** at RT in water, as shown in Scheme 24. As the reaction was ended, the catalyst was recovered and used further for 5 times. However, **1** with EWGs gave a higher yield of **38** compared to those with ERGs.

Similarly, Honari and co-workers[70] devised Fe_3O_4@nSiO_2@mSiO_2 immobilized with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and utilized it as a nanocatalyst (10 mg) to synthesize novel analogues of pyrazolo-pyrano[2,3-*d*]pyrimidinedione **38** by utilizing the same substrate scope (1 mmol) as shown in Scheme 24. As all the reactants were consumed, the reaction

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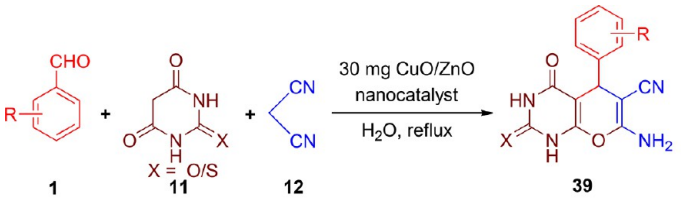
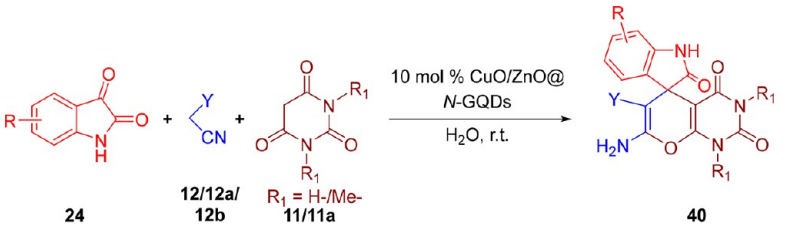
Scheme 25. Affording 39 Using ZnO-Supported CuO as a Nanocatalyst



Product 39: Yield = 88-92 %, Total Enrty = 16, Time = 10-40 min;
R = H-, 4-(NO_2)-, 3-(NO_2)-, 4-Cl-, 3-Cl-, 2,4-di-Cl-, 4-CN-, 3-(OH)-, 4-Br-, 4-Me-, 3-Me-, 4-(OMe)-, 3-(OMe)-, 4-F-, 4-Ph-CH_2-O-, 4-(CHO)-
(**1** = 1 mmol, **11** = 1 mmol, **12** = 1 mmol)

Scheme 26. Synthesizing 40 Using N-Doped Graphene Quantum Dots Modified with CuO/ZnO



Product 40: R_1 = H-, Y = -CN, Yield = 95-98 %, Total Entry = 5, Time = 10-25 min;
Y = -COOMe/-COOEt, Yield = 95-97 %, Total Entry = 6, Time = 15-35 min;
R_1 = Me-, Y = -CN, Yield = 90-97 %, Total Entry = 4, Time = 20-30 min;
Y = -COOMe/-COOEt, Yield = 91-94 %, Total Entry = 5, Time = 20-30 min;
R = H-, 5-Cl-, 5-Br-, 5-(NO_2)-, 5,7-di-Cl-; (**1** = 1 mmol, **12/12a/12b** = 1 mmol, **11/11a** = 1 mmol)

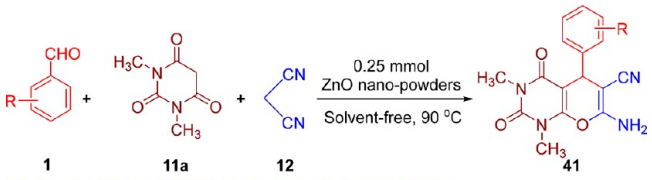
mixture was again refluxed for 2 min with continuous stirring. Thereafter, using an external magnet, the catalyst was recovered and reused for the next seven runs. **38** was recrystallized from hot ethanol, although various EWGs/ERGs on **1** of aryl aldehydes have no any quantifiable effect on the yield of **38**. In comparison to above 4-CR, here the main benefits are the higher yield and decreased reaction time.

3.1.2. Copper-Based NP-Catalyzed Synthesis. The heterogeneous ZnO-supported copper oxide nanoparticles were prepared by a coprecipitation method. This NPs were used as a catalyst (30 mg) by Albadi et al.[71] to synthesize **39** via reaction of diversified **1** (1 mmol), **11** (1 mmol), and **12** (1 mmol) in water under reflux (Scheme 25). The catalyst was reused five times. **39** was recrystallized using hot ethanol. The presence of ERGs/EWGs on **1** did not appreciably affect the isolated yield of **39**.

After a few years, Safaei-Ghomi et al.[72] developed spiropyranopyrimidinediones **40**. For this purpose, they used nitrogen-doped graphene quantum dots (GQDs) modified with copper oxide (0D)/zinc oxide (1D) as a promoter (10 mol %) and carried out a reaction between derivatives of **24** (1 mmol) with **12**/**12a**/**12b** (1 mmol) and derivatives of **11** (1 mmol) in water at RT (Scheme 26). This heterogeneous catalyst was prepared using the hydrothermal method. As the reaction was stopped, the pure **40** was attained followed by recrystallization with ethanol. The catalyst was recovered and reused continuously for the next seven runs. Various types of substituents present on isatin **24** did not affect the isolated yield of **40**. The size of methyl groups and steric hindrance in methyl cyanoacetate gave a lower yield of **40**. Compared to the above Cu-based NP-catalyzed reaction, in this reaction, the decreased reaction time and higher yield are the major merits of this reaction protocol.

3.1.3. Zinc-Based NP-Catalyzed Synthesis. Maleki and co-workers[73] carried out solvent-free single-pot equimolar (1 mmol) treatment of **1**, **11a**, and **12** in the presence of zinc oxide nanopowder as an efficient and environmentally safe promoter at 90 °C to get **41** (Scheme 27). The ZnO nanopowders possessed homogeneous size and shape. EWGs on **41** showed reactivity better than that with ERGs.

Scheme 27. Synthesis of 41 in the Absence of Solvent Using ZnO Nanopowder



Product 41: Yield = 78-98%, Total Entry = 8, Time = 1.5-4 h;
R = H-, 4-Me-, 4-Cl-, 3-(NO_2)-, 2,4-diCl-, 4-Br-, 4-F-, 3-Cl-
(**1** = 1 mmol, **11a** = 1 mmol, **12** = 1 mmol)

Afterward, Moosavi-Zare et al.[74] synthesized different analogues of **42** by using the nanostructured Schiff base complex nano-Zn[2-bromophenylsalicylaldimine methylpyranopyrazole]Cl_2 (i.e., nano-[Zn-2BSMP]Cl_2]) as catalyst. The equimolar (1 mmol) reaction between aryl aldehydes **1**, **12**, and **11**/**11a** were carried out in aqueous ethanol at 40 °C. The catalyst used here was recovered and reused prior to four times (Scheme 28). **1** with EWGs/ERGs reacted successfully and gave a higher yield in a shorter reaction time compared to that with a zinc-based NP-catalyzed reaction.

Tabassum et al.[75] described a one-pot synthetic protocol for analogues of **43** via three-component condensation of **1** (1 mmol) with **12** (1 mmol) and **11** (1 mmol) in the presence of ZnO@PEG nanocatalyst (100 mg) in greener solvent ethanol at 25 °C (Scheme 29). After termination of the reaction, the promoter was recollected and used again for the next six runs

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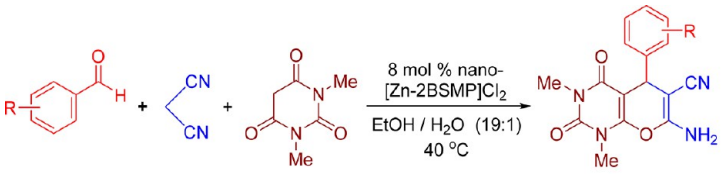
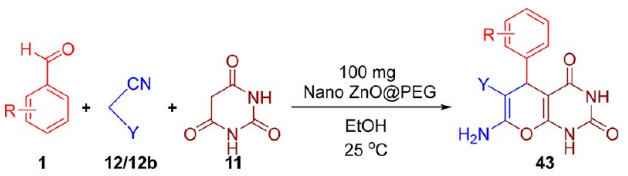
Scheme 28. [Zn-2-BSMP]Cl_2-Promoted Synthesis of 42



Product 42: Yield = 25-97%, Total Entry = 24, Time = 3-13 min;
R = 3-Br-, 2-Br-, 4-Cl-3-(NO_2)-, 4-(NO_2)-, H-, 4-F-, 3-(OH)-, 2,4-diCl, 2-Cl, 2,3-diCl-, 4-(CN)-, 4-Br-, 2-(NO_2)-, 3-(OMe)-, 4-Me-, 4-(OBn)-, 4-Cl-, 2-F-
(**11/11a** = 2 mmol, **1** = 1 mmol, **12** = 2.2 mmol)

Scheme 29. Nano-ZnO@PEG-Promoted Synthesis of 43



Product 43: Y = -CN, Yield = 91-96 %, Total Entry = 6, Time = 15 min;
Y = -COMe, Yield = 90-95 %, Total Entry = 6, Time = 15 min;
R_1 = 2-(OH)-5-Cl-, 2,3-di-Cl-, 2,4-di-Cl-, 2,6-di-Cl-, 3-(OH)-4-(OMe)-, 2-(OH)-4-(NO_2)-; (**1** = 1 mmol, **12/12a** = 1 mmol, **11** = 1 mmol)

with only a slight change in its efficiency. Various groups present on **1** did not affect the isolated yield of **43**. In this reaction, the authors changed the second substrate scope from the previous two zinc-based NP-catalyzed reactions and got **43**. Also, the reaction was completed in just 15 min and gave comparatively higher yield than the reaction catalyzed by ZnO nanopowders and nano-[Zn-2BSMP]Cl_2], respectively.

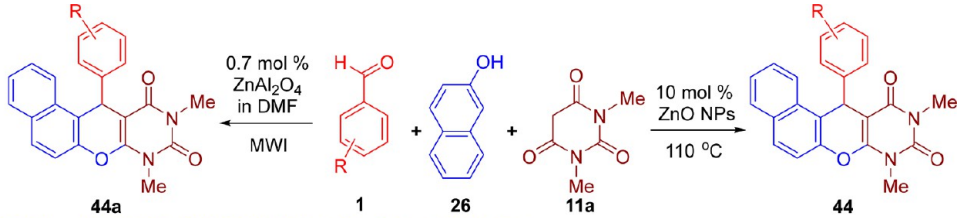
Mohaqeq and Ghomi[76] used Lewis acidic ZnO NPs (10 mol %) to synthesize a naphthopyranopyrimidinedione derivative, i.e., 8,10-dimethyl-12-aryl-9*H*-naphtho[1′,2′:5,6]-pyrano[2,3-*d*]pyrimidinedione **44** by treating discrete **1** (1.1 mmol) with **26** (1 mmol) and **11a** (1 mmol) at 110 °C with a lack of solvent, as shown in Scheme 30. In this regard, Mohaqeq et al.[77] synthesized novel analogues of **44a** using the same substrates by utilizing heterogeneous catalyst, $ZnAl_2O_4$ NPs (0.7 mol %), under microwave irradiation (MWI) of 500 W (Scheme 30). After reaction completion, the product **44a** was isolated from the crude mixture. However, in this case, the reaction was completed in slightly lower reaction time than the previous reported reaction, and also in both reactions, EWGs bearing aryl aldehydes gave higher yield (75−92%) compared to those bearing ERGs. In addition to this, in both reactions, the catalyst was recovered using an external magnet and used further for the next six runs.

An efficient heterogeneous nanocatalyst SCMNPs@uridine/Zn (20 mg) was utilized by Wei et al.[78] to develop tricyclipyranopyrimidinediones **45** via equimolar (1 mmol) treatment of **11**, **28**, **1**, and **12c** at 70 °C under solvent-free media (Scheme 31). The catalyst was reused for an extra six runs. From the remaining mixture, the pure **45** was obtained followed by recrystallization. The presence of various EWGs/ERGs did not have any measurable effects on the isolated yield of **45**. This group developed pyrazole-derived pyrano[2,3-*d*]pyrimidines. Here, the major benefits of this protocol include the used of solvent-free conditions.

3.1.4. Nickel-Based NP-Catalyzed Synthesis. Rajinder et al.[79] used immobilized nickel NPs supported by nitrogen-doped titania (i.e., nickel NPs@N-doped TiO_2, 100 mg) catalyzed equimolar (1 mmol) treatment of substituted **1**, **12a**, and **11** in methanol at 65 °C to afford **46** (Scheme 32). After reaction completion, the catalyst was recollected and used for extra five times continuously. **1** carrying ERGs reacted at a faster rate than those carrying EWGs and produced a high yield in a short time. It was noticed that aliphatic, heteryl, and unsaturated aryl aldehydes did not give the desired product. Sabbaghnasab and Sheikhhosseini[80] developed novel analogues of **47**. But in this case, instead of ethylcyanoacetate, they used malononitrile **12** which on treatment with **1** and **11** gave the product **47**. The reaction was catalyzed by nickel oxide NPs in water at 100 °C (Scheme 32, **47**), and compared to the above reaction, the major advantage is the decreased reaction time. The NiO NPs have uniform sphere shapes and sizes of less than 100 nm. **1** with various EWGs and ERGs reacted successfully in a shorter time.

Then Najafi et al.[81] prepared a Lewis acidic $NiCo_2O_4$@OCMC@Zn(BDC) as an efficient nanocomposite (10 mg) in the treatment of discrete **1** (1 mmol) with **11a** (1 mmol) and the yellow pigment curcumin **22** (1 mmol) as a naturally occurring 1,3-dicarbonyl compound which afforded **48** in aqueous ethanol under reflux (Scheme 33). As the reaction

Scheme 30. Synthesizing 44/44a Using ZnO NPs



Product 44: Yield = 75-95 %, Total Entry = 11, Time = 20-40 min;
Producr 44a: Yield = 75-92 %, Total Entry = 14, Time = 10-20 min;
R = 4-Br-, 4-(NO_2)-, H-, 4-Cl-, 4-F-, 4-Me-, 2,4-di-Cl-, 3-(NO_2)-, 3-Cl-, 3-(OMe)-, 2-Me-, 2-(OMe)-, 3-Me-, 1-Cl-; (**1** = 1.1 mmol, **26** = 1 mmol, **11a** = 1 mmol)

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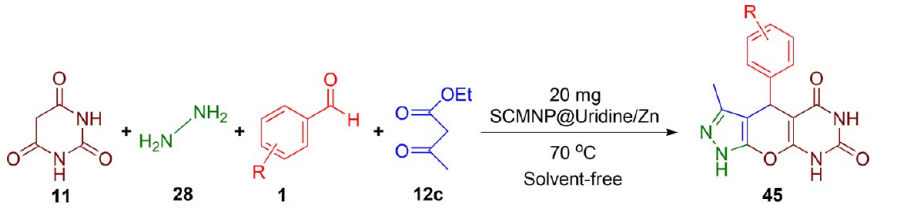
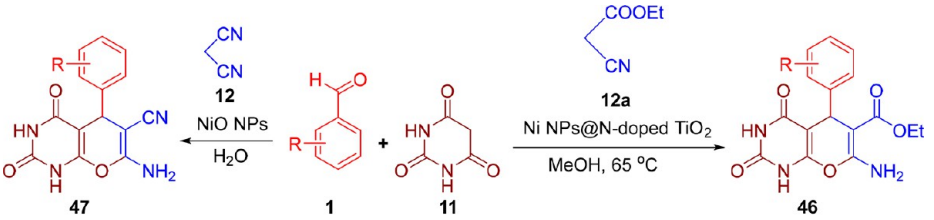
Scheme 31. Utilizing SCMNPs@Uridine/Zn as a Promoter in the Synthesis of 45



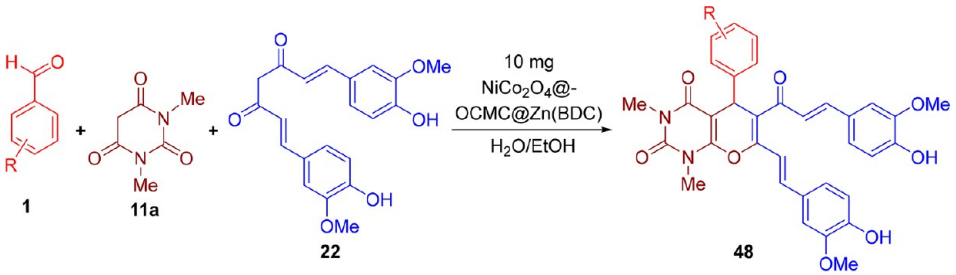
Product 45: Yield = 89-97 %, Total Entry = 16, Time = 15-35 min;
R = H-, 2-Cl-, 3-Cl-, 4-Cl-, 2,4-di-Cl-, 2-Br-, 3-Br-, 4-Br-, 2-(NO_2)-, 3-(NO_2)-,4-(NO_2)-, 2-(OMe)-, 4-(OMe)-, 2-(OH)-, 4-(OH)-3,5-di-(OMe)-, 4-Me-, 4-(NMe_2)-
(**11** = 1 mmol, **28** = 1 mmol, **1** = 1 mmol, **12c** = 1 mmol)

Scheme 32. N-Doped TiO_2-Ni NP- and NiO NP-Promoted Synthesis of 46 and 47



Product 46: Yield = 76-95 %, Total Entry = 10, Time = 30-90 min;
R = H-, 4-Me-, 4-(OMe)-, 4-(OH)-, 4-Cl-, 3,4-($OMe)_2$-, 3-(NO_2)-, 4-(NO_2)-, 4-Br-, 3-Br-;
Product 47: X = O,Yield = 37-78 %, Total Entry = 7, Time = 4-45 min;
X = S, Yield = 17-95 %, Total Entry = 5, Time = 5-20 min;
R = 4-(NMe_2)-, 3-(NO_2)-, 2,4-di-(OMe)-, 3,4,5-tri-(OMe)-, H-, 4-(OMe)-, 3-(OH)-
(**1** = 1 mmol, **11** = 1 mmol, **12a** = 1 mmol, Ni NPs = 100 mg)

Scheme 33. Synthesizing 48 by Using $NiCo_2O_4$@OCMC@Zn(BDC)



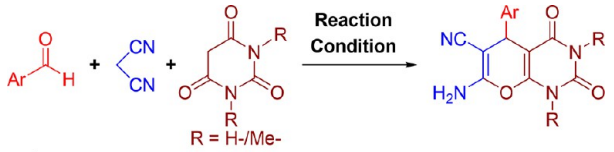
Product 48: Yield = 79-95 %, Total Entry = 8, Time = 4-6 min; (**1** = 21 mmol, **11a** = 1 mmol, **22** = 1 mmol)
R = 4-Cl-, 4-(NO_2)-, 3-(NO_2)-, 2,4-di-Cl-, 4-(CN)-, 3-(OH)-, 4-Br-, 4-(OMe)-

terminated, dichloromethane was added to the crude reaction mixture in which the catalyst remains insoluble and separated with the help of a magnet and was furthermore used without a loss of its effectiveness for the next six runs. **1** with EWGs gave a higher isolated yield of **48** than those with ERGs. The substrate used here, i.e., curcumin, is naturally occurring from the rhizome of turmeric.

3.1.5. Nanosilica-Based Synthesis. A common reaction protocol to synthesize pyrano[2,3-*d*]pyrimidine **49** is shown in Scheme 34 by the treatment of aryl aldehyde **1** (1 mmol), malononitrile **12** (1 mmol), and barbituric acid derivatives **11**/**11a** (1 mmol) using different reaction conditions.

Table 2 shows discrete reaction conditions to synthesize analogues of **49** from aromatic aldehyde **1**, malononitrile **12**, and barbituric acid/1,3-dimethyl barbituric acid **11**/**11a**. Here, various silica-based MNPs like SiO_2@Glu/$Si(OEt)_2(CH_2)_3N{=}Mo[Mo_5O_{18}]$, nanobasic silica, SnO_2/SiO_2, and nano-sized $[(DABCO)_2C_3H_5OH]$ $NiCl_4$ were reported to prepare derivatives of scaffold **49**. It is seen from the Table 2 that, in all of these reactions comparatively, a similar yield was obtained. The most advantageous feature of these reactions includes is

Scheme 34. General Scheme to Synthesize 49 Using Nanosilica-Based Catalysts



(**1** =1 mmol, **12** = 1 mmol, **11**/**11a** = 1 mmol)

show in entries 1−4, where the reaction time decreases. After reaction completion, the catalysts were recovered using an external magnet and reused for next several runs except catalyst shown in entry 2 which is the homogeneous catalyst. In all reactions, various ERGs or EWGs bearing aryl aldehydes did not affect the final yield of the product. In addition to this, in entry 2, aryl *ortho*-substituted aldehydes produced a higher yield than *para*-substituted aldehydes requiring a longer reaction time for completion due to steric hindrance at the *ortho*-position.

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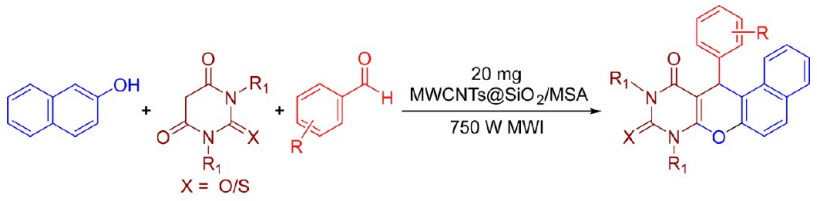
Table 2. Comparison Table for Nanosilica-Based Synthesis of Analogues of 49

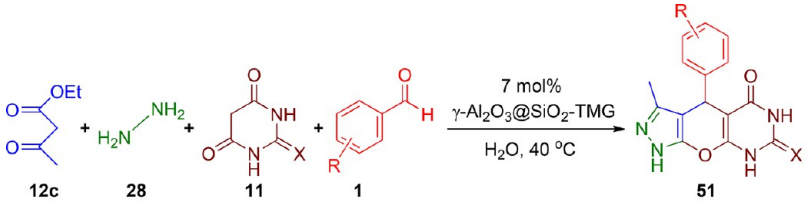
entry	reaction condition (catalyst, solvent, temperature)	yield (%)	reaction time	reusability of the catalyst	ref
1	4 mg of SiO_2@Glu/$Si(OEt)_2(CH_2)_3N{=}Mo[Mo_5O_{18}]$, solvent-free, 80 °C	90−95	10−40 min	10	Ghashag[82]
2	25 mol % of nanobasic silica, solvent-free, 90 °C	69−96	1−2 h		Yelwande and Lande[83]
3	15 wt % SnO_2/SiO_2, EtOH, RT	90−95	50−80 min	3	Ghasemzadeh et al.[81]
4	20 mg of nanosized $[(DABCO)_2C_3H_5OH]$ $NiCl_4$, Water, 70 °C	85−95	6−17 min	4	Pourkazemi et al.[84]

Scheme 35. MWCNT@SiO_2/MSA-Catalyzed Synthesis of 50



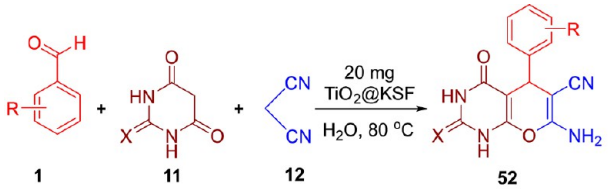
Product 50: X = O, R_1 = H-, Yield = 80-94 %, Total Entry = 6, Time = 20-35 min;
R_1 = Me-, Yield = 76-90 %, Total Entry = 5, Time = 20-40 min;
X = S, R_1 = H-, Yield = 80-85 %, Total Entry = 2, Time = 30 min;
R = H-, 2-Cl-, 4-Cl-, 4-(NO_2)-, 4-(OMe)-, 2-(OH)-5-(NO_2)-
(**26** = 1 mmol, **11/11a** = 1 mmol, **1** = 1 mmol)

Scheme 36. Tetramethylguanidine-Catalyzed Synthesis of 51



Product 51: X = O, Yield = 89-98 %, Total Entry = 10, Time = 10-20 min;
X = S, Yield = 85-98 %, Total Entry = 7, Time = 12-21 min;
R = H-, 2-(OMe)-, 3,4-di-(OMe)-, 4-Me-, 4-Cl-, 3-(NO_2)-,4-(NO_2)-, 4-(OH)-, 4-Br-, 3-Cl-, 2-Cl-, 3-(OH)-
(**12c** = 1 mmol, **28** = 1 mmol, **11** = 1mmol, **1** = 1 mmol)

Scheme 37. Synthesizing 52 with the Help of TiO_2@KSF



Product 52: X = O, Yield = 84-93%, Total Entry = 12, Time = 25-45 min;
X = S, Yield = 89-95%, Total Entry = 6, Time = 10-18
R = H-, 4-Br-, 3-(NO_2)-, 2-(NO_2)-, 4-Me-, 2-(OH)-, 4-Cl-, 3-Cl-, 2-Cl-, 4-F-, 4-(NO_2)-,4-OH-, 3-OH-, 4-(OMe)-, 4-(NMe_2)-; (**1** = 1 mmol, **11** = 1 mmol, **12** = 1 mmol)

Ahmadi et al.[85] utilized multiwalled carbon nanotube surface supported by meglumine sulfonic acid as a heterogeneous solid acid catalyst (20 mg) to synthesize a novel benzochromeno-pyrimidine **50** analogues via equimolar reaction of **26**, **11**/**11a**, and diversified **1** without solvent using MWI (Scheme 35). The catalyst was reused five time with only slight efficiency loss. Isolated yield of the pure **50** was achieved followed by recrystallization using ethanol. **1** bearing EWG reacted at faster rate in short time than those bearing ERG. However, sterically hindered aromatic aldehydes reacted successfully but takes relatively longer reaction time.

A nanosized organic−inorganic hybrid of γ-Al_2O_3 functionalized by tetramethylguanidine anchored with 3-chloropropyltrimethoxysilane could be used as a heterogeneous basic nanocatalyst (7 mol %), developed using the glycothermal method. This could be used as an impactful catalyst in the synthesis of analogues of **51** by M. Keshavarz et al.[86] which consisted of the reaction of **12c** (1 mmol), **28** (1 mmol), **11** (1 mmol), and **1** (1 mmol) at 40 °C (Scheme 36). As the reaction was terminated, the catalyst was separated and reused for the next run. The crude product was filtered, washed to get the pure product. An aryl aldehyde **1** with either an ERG/EWG did not affect the harvested product **51** considerably.

3.1.6. Titanium-Based NP-Catalyzed Synthesis. M. Mohammadi Zeydi et al.[87] developed a highly efficient and heterogeneous nano-TiO_2@KSF (20 mg) catalyzed synthesis of **52**'s analogues using the 3-CR of **1** (1 mmol), **11** (1 mmol), and **12** (1 mmol) in water under mild reaction conditions at 80

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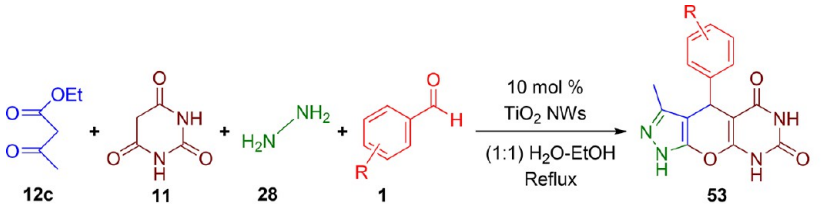
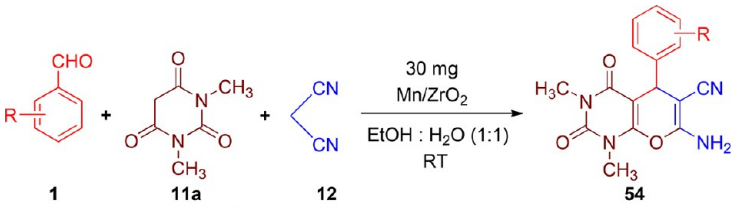
Scheme 38. Utilizing Titanium Dioxide Nanowires as a Promoter to Synthesize 53



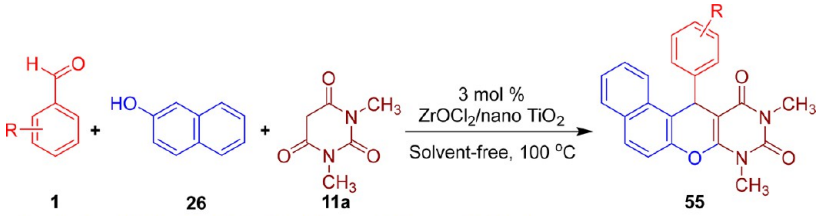
Product 53: Yield = 83-95 %, Total Entry = 12, Time = 45-100 min;
R = H-, 4-NO_2-, 2,4-di-Cl-, 4-Cl-, 4-(CN)-,4-(OMe)-, 4-^{i}Pr-, 4-(NEt_2)-, 3,4,5-tri-(OMe)-, 4-(OH)-, 2-Napthyl-, 2-Me-; (**12c** = 1 mmol, **11** = 1 mmol, **28** = 1 mmol, **1** = 1mmol)

Scheme 39. Construction of 54 Promoted by Mn/ZrO_2



Product 54: Yield = 79-90%, Total Entry = 11, Time = 1h;
R = 4-(OMe)-, 2,3-$(OMe)_2$-, 2,5-$(OMe)_2$-, 2-Br-, 4-Br-, 2-Cl-, 3-(NO_2)-, 3-(OH)-, H-, 2-F-, 3-F-
(**1** = 1 mmol, **11a** = 1mmol, **12** = 1.1 mmol)

Scheme 40. $ZrOCl_2$/Nano-TiO_2-Promoted Synthesis of 55 under Solvent-Free Conditions



Product 55: Yield = 80-85 %, Total Entry = 9, Time = 25-31 min,
R = 4-Br-, 4-(NO_2)-, H-, 4-Cl-, 4-F-, 4-Me-, 2,4-di-Cl-
(**1** = 1.1 mmol, **26** = 1 mmol, **11a** = 1 mmol)

°C (Scheme 37). This heterogeneous catalyst was reused for four times simultaneously with a small efficiency loss. However, the increased amount of catalyst did not affect the yield while shorter amounts of the catalyst lead to a lower yield. Aromatic aldehyde **1** containing EWG/ERG reacted in a shorter time and afford a higher yield of **52**.

S. Dastkhoon et al.[88] used TiO_2 nanowires (NWs) (10 mol %) as catalyst which afforded tricyclicpyrano[2,3-*d*] pyrimidine **53** through 4-CR of **12c** (1 mmol), **11** (1 mmol), **28** (1 mmol) and **1** (1 mmol) in water−ethanol under reflux (Scheme 38). After reaction termination, the recovered NWs were reused four times. Then the remaining reaction mixture was cooled to get the crude product **53** which then recrystallized from ethanol. **1** with EWG reacted faster and gave higher yield of **53** than those with ERG.

3.1.7. Zirconium-Based NP-Catalyzed Synthesis. Maddila et al.[89] gave synthesis of **54** by treating **1** (1 mmol), **11a** (1 mmol) and **12** (1 mmol) utilizing manganese doped zirconia (30 mg) catalyst in mixture of ethanol−water as solvent (Scheme 39). This heterogeneous catalyst has both Brønsted and Lewis acid centers and was stable in both alkaline and acidic solutions and reused up to six time continuously with small loss of its efficiency. Shorter reaction time, cost-effectiveness, and use of green solvent are some of the advantages of this synthetic pathways.

M. Mohaqeq et al.[90] have obtained naphthopyranopyrimidine derivatives, **55** using an efficient and reusable $ZrOCl_2$ supported on nano-TiO_2 catalyzed (3 mol %) one-pot synthetic way through a 3-CR of distinct aromatic aldehydes **1** (1 mmol), **26** (1 mmol) and **11a** (1 mmol) at 100 °C without solvent (Scheme 40). The lowered reaction time was the major merit of this protocol in comparison to previous reaction protocol. However, electronic nature of various substituents on an aromatic ring of an aldehyde did not considerably affects the isolated yield of the product.

3.1.8. Yttrium NP-Catalyzed Synthesis. R. P. Pawar et al.[91] developed recyclable heterogeneous yttrium oxide (10 mol %) catalyzed synthetic protocol to synthesize 7-amino-5-phenyl-substituted-1*H*-pyrano[2,3-*d*]-pyrimidine-2,4(3*H*, 5*H*)-dione analogues **56** via treating **1** (1 mmol), **11** (1 mmol) and **12** (1 mmol) in water−methanol media at 50 °C (Scheme 41). The catalyst used here was reused until three consecutive runs, after that isolated yield of **56** got decrease. In absence of a catalyst also, the reaction took place but only a trace amount of **56** was formed. **1** containing either EWG/ERG at any position did not alter the yield of the reaction and gave high yield. The major advantages of this method involve the use of minimized reaction temperature, use of nontoxic catalyst, and high yield of product.

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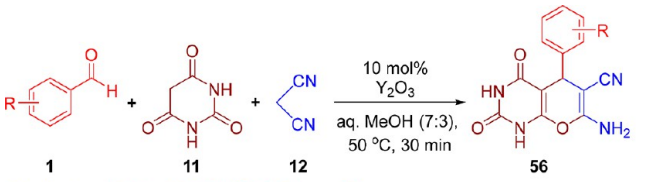
Scheme 41. Synthesis of 56 Using Y_2O_3 NPs



Product 56: Yield = 88-95%, Total Entry = 15;
R = H-, 4-(NO_2)-, 4-Br-, 4-(OH)-, 2-Cl-, 2,4-$(OMe)_2$-, 2-(NO_2)-, 3-(NO_2)-, 3,4-$(OMe)_2$-, 4-(OMe)-, 4-Me-, 4-Cl-, 3-Me-, 3-Br-, 2-(OMe)-
(**1** = 1 mmol, **11** = 1 mmol, **12** = 1 mmol)

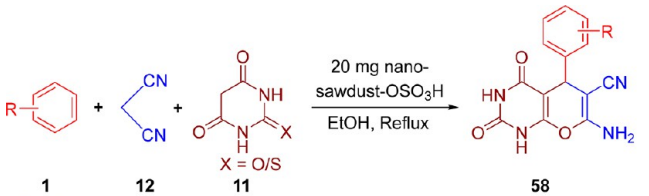
3.1.9. Organic Nanocatalyst-Based Synthesis. A. Khazaei and his co-workers[92] have used water-mediated protocol to synthesize **57**. A Domino-Knoevenagel-Michael cyclo-condensation reaction of **1** (2 mmol), **12** (2.2 mmol) and **11**/**11a** (2 mmol) in the presence of Brønsted acidic nanotitania sulfuric acid (TSA, 20 mg) or boric acid (10 mol %) in aqueous solution as a catalyst and water−ethanol or tetrahydrofuran-water as a solvent under reflux (Scheme 42). Boric acid abstracted hydroxide ion from water and generated proton or releasing of a proton by nano-TSA can efficiently catalyze the reaction. Discrete derivatives of **1** carrying of either ERG/EWG and halogens could efficiently be utilized in the reaction which gives a higher isolated yield of **57**. As the reaction was terminated, the nano-TSA was distinguished from the crude mixture and recrystallized with a ethanol−water to get the pure **57**.

In this regards, B. Sadeghi et al.[93] have also reported a green and cost-effective sawdust-OSO_3H NPs-catalyzed (20 mg) 3-CR of substituted **1** (1 mmol), **12** (1 mmol) and **11** (1 mmol) in ethanol under reflux conditions afforded a novel **58**'s analogues (Scheme 43). This solid acidic nanocatalyst (size <100 nm) has increased surface polarity and acidity which improves the efficiency. The nature (electronic) and place of discrete groups on **1** did not alter the yield of **58**.

The similar pyrano[2,3-*d*]pyrimidine's analogues were also obtained by various groups which are described in Table 3 (entryies 1−6) by using the same substrate scope as shown in Scheme 44.

Table 3 shows various reaction conditions to develop pyrano[2,3-*d*]pyrimidine's derivatives **59** via the treatment of aryl aldehyde **1** with malononitrile **12** and barbituric acid/thiobarbituric acid **11**. All three reactants were taken in equimolar amount (1 mmol) except for entry 1 where **1** (1

Scheme 43. Synthesis of 58 by Utilizing Nano-Sawdust-OSO_3H

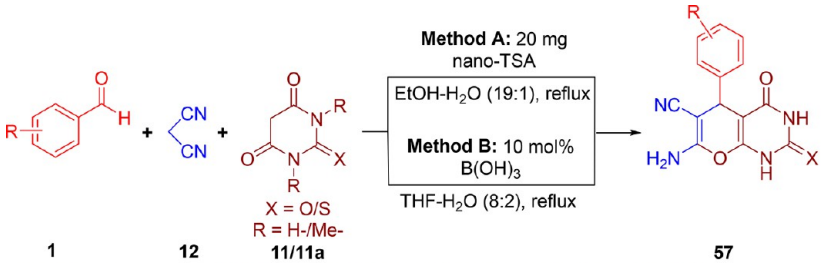


Product 58: X = O, Yield = 85-94%, Total Entry = 8, Time = 8-20 min;
X = S, Yield = 69-83%, Total Entry = 4, Time = 20-25 min;
R = 4-Me-, 3-(NO_2)-, 3-Cl-, 4-(NO_2)-, H-, 4-Cl-, 2-Cl-, 4-Br-, 4-(OMe)-
(**1** = 1 mmol, **12** = 1 mmol, **11** = 1 mmol)

mmol), **12** (1.1 mmol) and **11** (1 mmol), and also for entry 2 only X = O/S otherwise for all entries X = O. Herein, we have covered different reported organo nanocatalysts such as NS-C_4(DABCO−$SO_3H)_2$·4Cl, Nano-Cellulose-$SbCl_5$, Mica/Fe_3O_4, Nanocellulose-OSO_3H, $SbCl_5$/nanosawdust and Nano-BF_2O-coconut shell. All of these are heterogeneous catalysts. This table also shows methodologies to synthesize 6-CN, 6-COOEt and both analogs of **59**. It can be observed from the Table 3 that by changing the reaction conditions, affects isolated yield of the product and time of reaction. From entry 1−3, the main benefit of the third is that, the reaction was carried out at RT in just 10 min with high yield. Compared to third entry, in first and second entry, though the time is less but still reflux temperature were required. Thereafter, B. Sadeghi et al.[97,98] have obtained ester derivatives of pyrano-[2,3-*d*]pyrimidinone at sixth position. In addition, in both reactions comparatively similar yield were gained with almost similar time interval. Then Molaei and Sadeghi[99] used nano-BF_2O-coconut shell as catalyst and attained **59**'s analogues. Using the same substrate scope as shown in Scheme 45. In entry 6, **59**'s analog were achieved in lower reaction time compared to Entries 4 and 5. Instead in all these reactions, the electronic nature of various EWG/ERG did not affects the isolated yield of the product quantifiably.

J. Zhang et al.[100] described SCMNPs@Urea/Py-$CuCl_2$ catalyst and synthesized **62** and pyrano[2,3-*d*]-pyrimidine-2,4,7-trione **61** using 3-CR of discrete aryl aldehyde **1** (1 mmol) with **11** (1 mmol) and **12** (1.1 mmol) or 2, 2-dimethyl-1,3-dioxane-4,6-dione **60** (1 mmol) in aqueous ethanol or water as a solvent (Scheme 45). After reaction completion, the crude reaction mixture was cooled to RT. Then the catalyst was recovered via use of an external magnet as well as the

Scheme 42. Nano-TSA and Boric-Acid-Catalyzed Synthesis of 57



Product 57: Method A, R_1 = H-, Yield = 53-91 %, Total Entry = 10, Time = 57-100 min;
R_1 = Me-, Yield = 79-88 %, Total Entry = 5, time = 21-47 min;
Method B, R_1 = H-, Yield = 65-90 %, Total Entry = 10, Time = 57-142 min;
R_2 = Me-, Yield = 82-88 %, Total Entry = 5, Time = 25-65 min;
R = H-, 4-Cl-, 4-Me-, 3-(NO_2)-, 2-Cl-, 4-(OMe)-, 2-(OMe)-, 2,4-di-Cl-, 3-Me-, 4-(NO_2)-, 4-Me-
(**1** = 2 mmol, **12** = 2.2 mmol, **11**/**11a** = 2 mmol)

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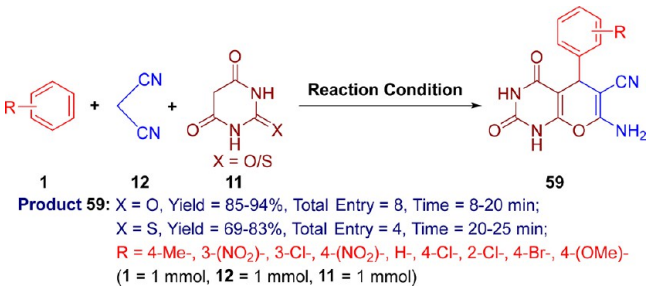
Table 3. Various Synthetic Routes to Prepare Analogues of 59 Using Different Organic Nanocatalysts

entry	reaction conditions (catalyst, solvent, temperature)	yield (%)	reaction time (min)	reusability of the catalyst	ref
	6-CN derivatives				
1	5 mol % of NS-C_4(DABCO-SO_3H)$_2$·4Cl, H_2O, 80 °C	90−96	5−8	5	Goli-Jolodar and Shirini[94]
2	nanoCellulose-$SbCl_5$ (30 mg), EtOH, reflux	86−97	5−10	3	Sadeghi et al.[95]
3	mica/Fe_3O_4 (3 mg), EtOH, RT	82−98	10		Maleki et al.[96]
	6-COOEt derivatives				
4	nanocellulose-OSO_3H (8 mg), aq EtOH, RT	86−93	40−55	several	Sadeghi et al.[97]
5	$SbCl_5$/nanosawdust (20 mg), aq EtOH(1:1), RT	88−93	40−50	3	Sadeghi et al.[98]
	6-CN/6-COOEt derivatives				
6	nano-BF_2O-coconut shell (15 mg), EtOH, reflux	87−94	15	4	Molaei and Sadeghi et al.[99]

Scheme 44. General Reaction Scheme for Organic Nanocatalyst-Based Synthesis of Analogues of 59



isolated yield of the products **61** or **62** was recrystallized from aqueous ethanol. The electronic nature and position of various ERG/EWG on **1** was not affected the isolated yield of both products.

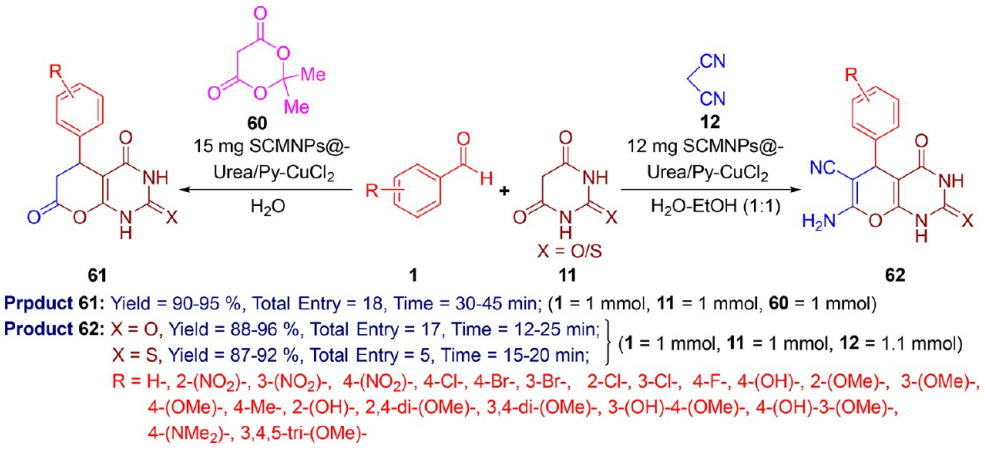
A nanoporous solid acid catalyst, sulfonic acid functionalized SBA-15 (20 mg) utilized by G. M. Ziarani et al.[101] This group synthesized spiropyranopyrimidine derivatives **63** through the equimolar (2 mmol) reaction of **24** with malononitrile derivative **12**/**12a**/**12b** and **11**/**11a** in the presence of SBA-Pr-SO_3H (Scheme 46). However, the reaction was carried out under solvent-free condition and they also obtained 6-cyano, 6-methyl- and 6-ethyl ester derivatives of spiropyranopyrimidine. Then the reaction mixture was added in hot ethanol and acetonitrile. Then it was filtered to recover the catalyst and pure product **63** attained from filtrate.

Khodabakshi et al.[102] used multiwalled carbon nanotube (5 mg) for the first time as heterogeneous catalyst to synthesize the fused heterocyclic scaffolds, **64** through four-component reaction of **12c** (1 mmol), **28** (1 mmol), diverse **1** (1 mmol) and **11** (1 mmol) in equimolar mixture of aqueous alcohol (Scheme 47). The crude product precipitated was recrystallized using ethanol. The catalyst separated via filteration was dried under vacuume for 24 h at 100 °C and reused without loss of efficiency up to eight runs continuously. The overall isolated yield of **64** was not appreciably affected by the presence of different substitution on an aromatic ring **1**. In spiropyranopyrimidine and pyrazolopyranopyrimidine derivatives, relatively higher yield was attained in case of pyrazolopyranopyrimidine than spiro derivatives.

3.1.10. Metal Nanocatalyst. Vaid et al.[103] elaborated nanosized heterogeneous solid base metal-catalyst, calcined mixed oxide-supported alkali metal, i.e., K_2O/Al_2O_3-CaO (50 mg) via a mechanical grinding technique and utilized it in the synthesis of **65** through a Michael addition followed by Knoevenagel reaction between **1** (1 mmol) with **12** (1 mmol) and **11** (1 mmol) in acetonitrile as a solvent at 80 °C (Scheme 48). At the end, ethyl acetate was added into reaction mixture slow down the reaction and recover it. Which was then washed with ethyl acetate and dobled distilled water and dried. The pure **65** was obtained through solvent evaporation and was recrystallized from ethanol. Various analogues of **1** having electron-withdrawing substituents gave higher isolated yield of **65** than those with electron-releasing substituents. The most advantageous feature of this protocol includes the use of mechanical grinding method to prepare the nanocatalyst and its reusability up to five continuous runs.

Recently, Shehab and co-workers[104] synthesized novel pyrano[2,3-*d*]pyrimidines **66** and their derivatives using an efficient NPs as catalyst via the treatment of pyrrole-2-carboxaldehyde **1a** (0.005 mol) with **11** (0.01 mol) and **12**

Scheme 45. Synthesis of 61 and 62 through SCMNPs@Urea/Py-$CuCl_2$ as Catalyst



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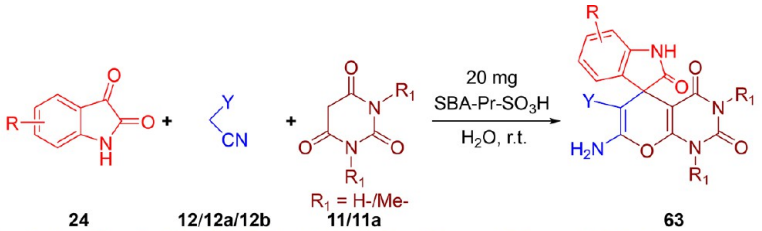
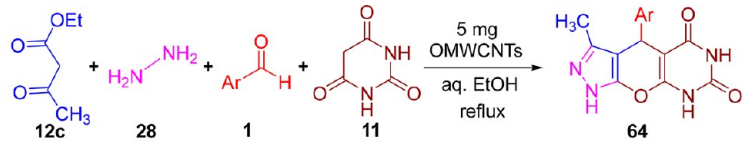
Scheme 46. Synthesis of 63 in the Presence of SBA-15 Functionalized by Sulfonic Acid



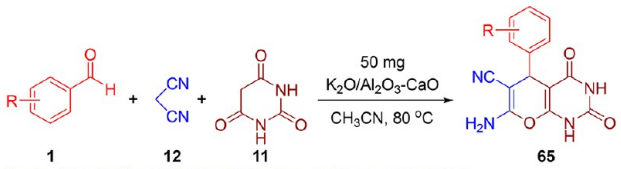
Product 63: R_1 = H-, Y = -CN, Yield = 86-91 %, Total Entry = 4, Time = 25-80 min;
Y = -COOMe/-COOEt, Yield = 77-95 %, Total Entry = 5, Time = 30-80 min;
R_1 = Me-, Y = -CN, Yield = 86-91 %, Total Entry = 2, Time = 55-80 min;
Y = -COOMe/-COOEt, Yield = 76-84 %, Total Entry = 4, Time = 30-110 min;
R = H-, 5-Cl-, 5-Br-, 5-(NO_2)-, 5,7-di-Cl-; (**24** = 2 mmol, **12/12a/12b** = 2 mmol, **11/11a** = 2 mmol)

Scheme 47. Multiwalled Carbon-Nanotube-Catalyzed Synthesis of 64



Product 64: Yield = 85-94 %, Total Entry = 12, Time = 65-100 min;
Ar = C_6H_5-, 4-(NO_2)-C_6H_4-, 2,4-di-Cl-C_2H_3-, 4-Cl-C_6H_4-, 4-(CN)-C_6H_4-, 4-(OMe)-C_6H_4-, 4-^{i}Pr-C_6H_4-, 4-(NMe_2)-C_6H_4-, 2,4,6-tri-(OMe)-C_6H_2-, 4-(OH)-C_6H_4-, 2-Naphthyl-, 2-Me-C_6H_4-
(**12c** = 1 mmol, **28** = 1 mmol, **1** = 1 mmol, **11** = 1 mmol)

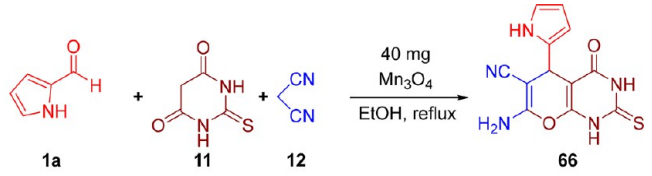
Scheme 48. K_2O/Al_2O_3-Calcined CaO-Promoted Synthesis of 65



Product 65: Yield = 85-95 %, Total Entry = 9, Time = 1.30-3.10 h;
R = H-, 4-Me-, 4-(OMe)-, 3,4-di-(OMe)-,3-(NO_2)-, 4-(NO_2)-, 4-Cl-, 4-Br-, 2-Cl-
(**1** = 1 mmol, **12** = 1 mmol, **11** = 1mmol)

(0.005 mol) in ethanol under reflux condition in 2 h (Scheme 49). They have used three types of catalysts, Fe_3O_4, ZnO and Mn_3O_4. Out of which Mn_3O_4 (40 mg) showed the best results. The fine powder of nanocrystals, Mn_3O_4, ZnO, Fe_3O_4 was dispersed on carbon-coated copper grid in ethanol. The recovered catalyst was reused up to next six suns. All the above-discussed MNPs catalyzed synthesis of pyrano[2,3-*d*]pyrimidine only. Only this group have synthesized acyclic and cyclic nucleosides derivatives of pyrano[2,3-*d*]pyrimidines. In the synthesis of **66**'s nucleoside analogue, by changing the reaction conditions, the product was changed.

Scheme 49. Mn_3O_4-Promoted Synthesis of 66



Product 66: Yield = 85 %, Total Entry =1, Time = 2 h
(**1a** = 0.005 mol, **11** = 0.01 mol, **12** = 0.005 mol)

3.2. Organocatalyzed Synthesis. Organocatalysts were acquired naturally or synthesized in the laboratory. Due to low or nontoxicity, low sensitivity to water and atmospheric oxygen, and easy manipulation and inexpensiveness of organocatalysts thus replacing metal-based catalysts.[105] Some of them were acquired either from nature or synthesized in the laboratory. As organocatalyst inexpensive, natural, nontoxic, efficient, commercially available,[106] their use in organic synthesis increase in recent years.

3.2.1. Acidic Organocatalyzed Synthesis. Various acidic organocatalysts including trichloroisocyanuric acid (TCCA), lactic acid, L-proline, acetic acid, etc. are discussed in this subsection. In this regard, Balalaie et al.[107] used environmentally benign amino acid as a neutral difunctional catalyst, L-proline. They devised the synthesis of well-functionalized analogues of **67** by using a three-component reaction between discrete **1** with an active methylene compound **12** and **11** in

Scheme 50. Various Synthetic Routes for the Production of Pyrano[2,3-d]pyrimidine 67

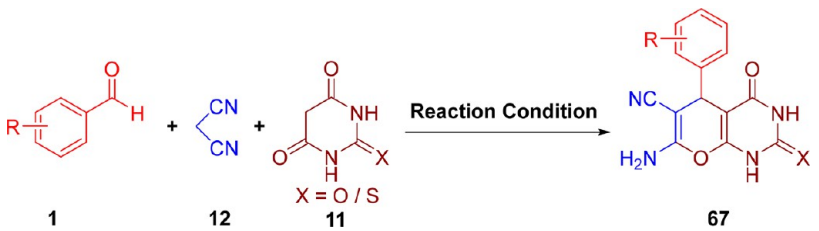


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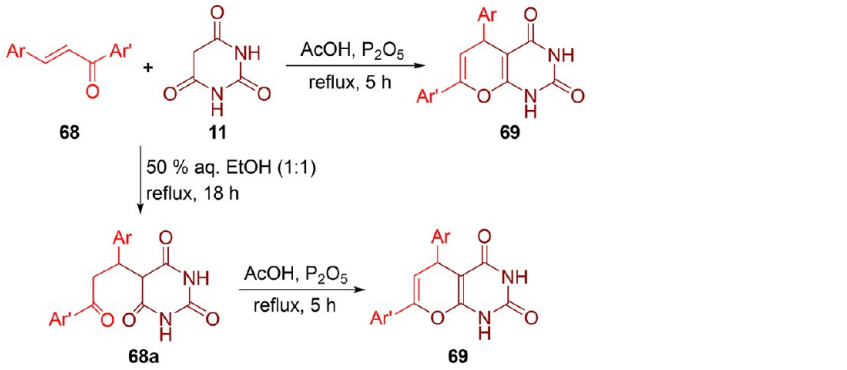
Table 4. Different Reaction Conditions for the Production of Pyrano[2,3-*d*]pyrimidine 67

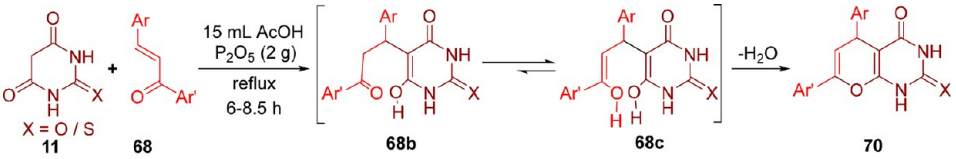
entry	reaction condition (catalyst, solvent, temperature)	yield (%)	reaction time	ref
1	5 mol % of L-proline, aq EtOH (1:1), RT	68−86	30−90 min	Balalaie et al.[107]
2	10 mol % trichloroisocyanuric acid, water	85−95	1.5−5 h	Deshmukh et al.[108]
3	aspartic acid (20 mol %), aq EtOH, RT	90−94	1.5−2.5 h	Ahad and Farooqui[109]
4	20 mol % of taurine, water, reflux	80−94	40−90 min	Shirini et al.[110]
5	0.3 g of mefenamic acid, EtOH, reflux	90−98	15−45 min	Sheikhhosseini et al.[111]

Scheme 51. Acetic Acid, P_2O_5-Catalyzed Synthesis of 69



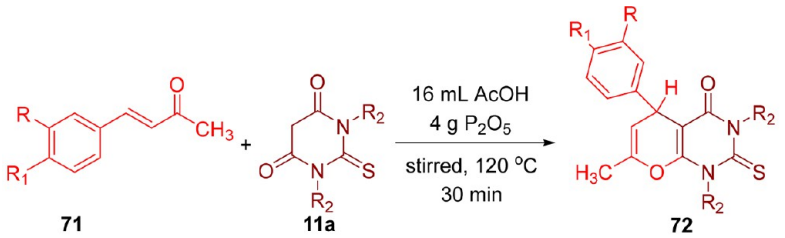
Product 69: Yield = 79-81 %, Total Entry = 4; (**68** = 5 mmol, **11** = 5 mmol, AcOH = 15 mL, P_2O_5 =2 g)
Ar = C_6H_5-, 4-Cl-C_6H_4-, 4-Me-C_6H_4-; Ar' = C_6H_5-, 4-(OMe)-C_6H_4-, 4-(NO_2)-C_6H_4-

Scheme 52. Use of AcOH, P_2O_5 as Catalyst to Afford 70



Product 70: X = O, Yield = 58-77 % , Total Entry = 3, Time = 6-8.5 h;
X = S, Yield =52-76 %, Total Entry = 3, Time = 6-8.5 h;
Ar = 4-Cl-C_6H_4-, Ar' = C_6H_5-, 4-Me-C_6H_4, 4-(NO_2)-C_6H_4-; (**11** = 5 mmol, **68** = 5 mmol)

Scheme 53. Utilizing AcOH in the Synthesis of 72



Product 72: Yield = 75-92 %, Total Entry = 25;
R = Ph-, H-, 2-Me-Ph-, 3-Me-Ph-, 2-(OMe)-Ph-, 3-(OMe)-Ph-, 4-(OMe)-Ph-;
R_1 = H-, MeO-; R_2 = MeO-, Me-, H-; (**71** = 5 mmol, **11a** = 5 mmol)

the presence of L-proline in water and ethanol at RT (Scheme 50). However, without use of the catalyst, in a solution with pH = 7, there was no reaction. **1** with either EWGs or ERGs had no significant effect on an isolated yield of product **67**.

Some other groups have also synthesized **67** by utilizing the same substrate scope as shown in Scheme 50 under different reaction conditions (Table 4).

Table 4 shows different reaction conditions to synthesize **67** using the treatment of aryl aldehyde **1**, malononitrile **12**, and barbituric/thiobarbituric acid **11**/**11a** for all entries in Table 4, with **1** (1 mmol), **12** (1.1/1.2 mmol), and **11** (1 mmol). Various acidic organocatalysts reported to prepare **67** are L-proline trichloroisocyanuric acid, aspartic acid, taurine and mefenamic acid. In it only Entry 4 have X = O/S (barbituric/thiobarbituric acid), otherwise in all entries X = O (barbituric acid). An observation from Table 4 showed that, from entries 1−5 isolated yield of **67** is increased. Trichloroisocyanuric acid and aspartic acid catalyzed synthesis of **67** took longer time than others. Mefenamic acid promoted reaction gave highest yield of product **67** in shortest reaction time compared to others. In all of these reactions, various EWGs/ERGs on an aryl aldehyde did not considerably affect the isolated yield of product **67**.

Ahmed et al.[112] synthesized a novel derivative of 5,7-diaryl-1,2,3,4-tetrahydro-2,4-dioxo-5*H*-pyrano[2,3-*d*]-pyrimidines **69** (Scheme 51). They used two methods: First, benzylidene-

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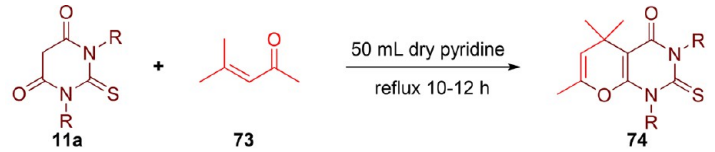
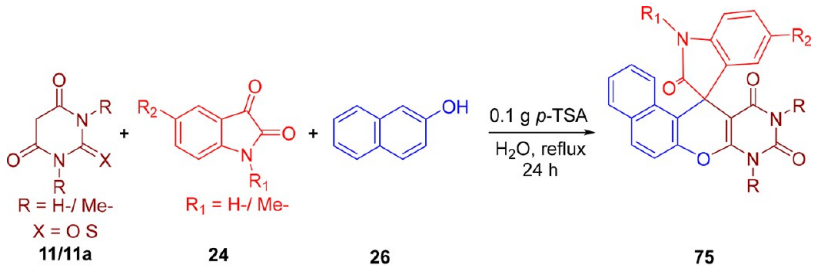
Scheme 54. Synthesizing 74 Using AcOH-P_2O_5



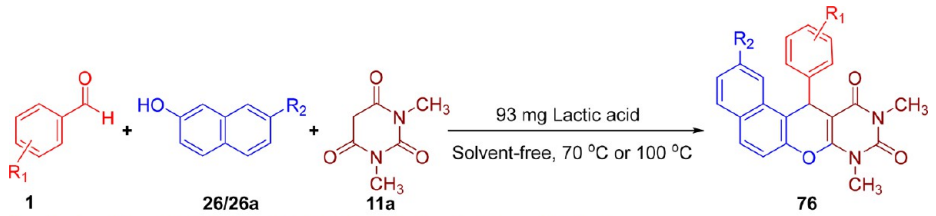
Product 74: Yield = 85.4-90.5 %, Total Entry = 7; (**11a** = 5 mmol, **73** = 5 mmol)
R = C_6H_5-, 2-Me-C_6H_4-, 3-Me-C_6H_4-, 4-Me-C_6H_4-, 2-(OMe)-C_6H_4-, 3-(OMe)-C_6H_4-, 4-(OMe)-C_6H_4-

Scheme 55. *p*-TSA-Catalyzed Synthesis of 75



Product 75: X = O, Yield = 77-85 %, Total Entry = 6; X =S, Yield = 80-82 %, Total Entry = 3;
R_2 = H-, Br-; (**11/11a** = 1 mmol, **24** = 1 mmol, **26** = 1 mmol)

Scheme 56. Lactic-Acid-Promoted Synthesis of 76 without Solvent



Product 76: R_2 = -OH, Yield = 87-93 %, Total Entry = 9, Time = 40-50 min;
R_2 = -H, Yield = 81-95 %, Total Entry = 8, Time = 20-35 min;
R_1 = H-, 2-Cl-, 3-Cl-, 4-Cl-, 4-F-, 2-(NO_2)-, 4-(CN)-, 3-(NO_2)-, 2-F-, 4-Br-
(**1** = 1 mmol, **26/26a** = 1 mmol, **11a** = 1 mmol)

acetophenone **68** (5 mmol) reacted with **11** (5 mmol) in 15 mL of AcOH with phosphorus pentoxide (2 g) and was refluxed at 120 °C for 5 h. The crude product was obtained by treating the mixture with crushed ice and then filtered, washed, and recrystallized from benzene. Second, **68** was treated with **11** in rectified spirit and water under reflux for 18 h to get **68a**, which then underwent cyclization in acetic acid and phosphorus pentoxide to get **69**. After completion, R-spirit was used to recrystallize the crude product **69**.

Rahman et al.[113] have also synthesized other analogues of **70** by reacting arylidene-acetophenone **68** (5 mmol) with **11** (5 mmol) in 15 mL of AcOH with P_2O_5 (2 g) under reflux condition for 6−8.5 h at 135−140 °C to get the intermediate **68b** and **68c** which was then undergo cyclization to get **70** (Scheme 52). After reaction completion, the pure product was obtained via recrystallization using R-spirit. The shorter reaction time of this protocol is more beneficial against the previous reaction protocol.

Ahluwalia et al.[114] used phosphorus pentoxide and synthesized 1,3,5-triaryl-1,2,3,4-tetrahydro-4-oxo-7-methyl-2-thioxo-5*H*-pyrano[2,3-*d*]-pyrimidine **72** (Scheme 53) by the condensation reaction of the mixture of 1,3-diphenyl-2-thiobarbituric acid **11a** (5 mmol) with distinctly substituted benzylideneacetone **71** (5 mmol) was stirred in 16 mL glacial acetic acid along with 4 g P_2O_5. The solid product **72** was obtained through crushed ice which was then filtered, washed, and purified using eluent benzene in column chromatography, and benzene-petroleum ether was used to get the purified product.

Ahluwalia et al.[115] also synthesized 1,3-diaryl-1,2,3,4-tetrahydro-5,7,7-trimethyl-4-oxo-2-thioxo-7*H*, **74**. The reaction of 1,3-disubstituted barbituric acid **11a** (5 mmol) with mesityl oxide **73** (5 mmol) in dry pyridine (50 mL) under reflux of 10−12 h generated **74** (Scheme 54). After termination of the process, the isolated yield of **74** was recrystallized from methanol as a yellow solid.

Bazgir et al.[116] described a green and environmentally friendly one-pot synthetic route for spironaphthopyrano[2,3-*d*]-pyrimidine-5,3′-indolines **75** by a three-component cyclo-condensation reaction of **11**/**11a** (1 mmol) with **24** (1 mmol) and **26** (1 mmol) using *p*-TSA (0.1 g) catalyst in water at reflux (Scheme 55). However, the reaction also proceeded without catalyst but only a trace amount of the product was obtained after 2 days.

Sadeh with his co-workers[106] have developed a facile reaction protocol to synthesize the novel naphthopyranopyrimidines **76** catalyzed by lactic acid via a one-pot, 3-CR condensation of diversified **1** (1 mmol), **26**/**26a** (1 mmol), and **11a** (1 mmol) in lactic acid (0.093 g) under the solvent-free condition at 70 or 100 °C (Scheme 56). After reaction termination, **76** was separated from the mixture and recrystallized from ethanol.

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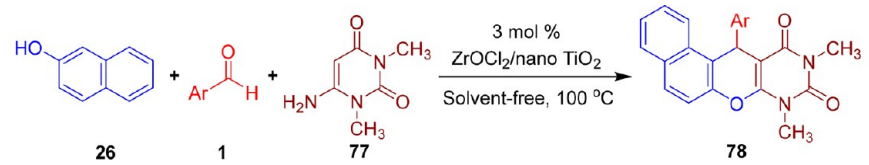
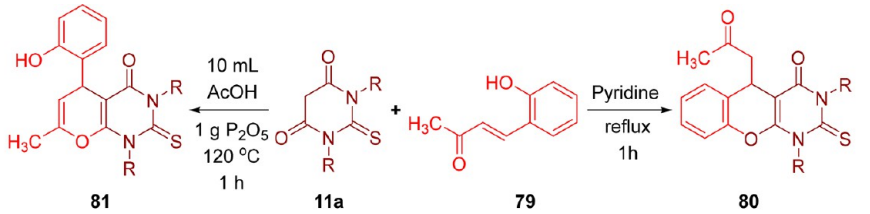
Scheme 57. Synthesis of 78 via Utilization of Lactic Acid



26 1 77 78

Product 78: Yield = 84-95 %, Total Entry = 19, Time = 20-45 min;
Ar = C_6H_5-, 2-Cl-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2,4-di-Cl-C_6H_3-, 4-F-C_6H_4-, 4-Br-C_6H_4-, 2-(NO_2)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NO_2)-C_6H_4-, 3-(OH)-C_6H_4-, 4-Me-C_6H_4-, 4-(OMe)-C_6H_4-, 4-(CN)-C_6H_4-, 2-Nap-, 2-F-C_6H_4-, 3-Br-C_6H_4-, 3-F-C_6H_4-, 4-(OH)-3-(OMe)-C_6H_3-; (Equimolar = 1 mmol = **26** = **1** = **77**)

Scheme 58. Synthesizing 80 and 81 Using Py and AcOH-P_2O_5, Respectively



81 11a 79 80

Product 80: Total Entry = 8, (**11a** = 1 mmol, **79** = 0.5 mmol); **Product 81:** Total Entry = 4; (**11a** = 1.54 mmol, **79** = 1.54 mmol)
R = 4-Me-C_6H_4-, 2-(OMe)-C_6H_4-, 3-(OMe)-C_6H_4-, C_6H_5-, 2-Me-C_6H_4-, 3-Me-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-

Fatahpour et al.[117] reported L-proline as catalyzed to afford other analogues of **76**, i.e., 8,10-dimethyl-12-aryl-12*H*-naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-9,11-dione **78** through the reaction of **26** (1 mmol) with substituted **1** (1 mmol) and *N*,*N*-dimethyl-6-amino-uracil **77** (1 mmol) at 100 °C (Scheme 57). After reaction termination, the pure **78** was attained followed by recrystallization with ethanol. However, in both reactions, aromatic aldehydes **1** bearing various electron-releasing or -withdrawing substituents had no explicit effect on the isolated yield of **78**.

Additionally, Ahluwalia and co-workers[118] synthesized a novel derivatives of 1,3-bis(substituted-phenyl)-5-(2-oxopropyl)-4-oxo-1,2,3,4-tetrahydro-2-thioxo-5*H*-benzopyrano[2,3-*d*]-pyrimidine **80** and 1,3-bis(substituted- phenyl)-5-(2′-hydroxyphenyl)-7-methyl-4-oxo-1,2,3,4-tetrahydro-2-thioxo-5*H*-pyrano-[2,3-*d*]-pyrimidindione **81**, respectively (Scheme 58). They used a condensation treatment of 1,3-bis(4-methylphenyl)-2-thiobarbituric acid **11a** (1 mmol) and *o*-hydroxy-benzylideneacetone **79** (0.5 mmol) in pyridine as a base under reflux for 1 h to afford product **80**, and in 10 mL glacial acetic acid with phosphorus pentoxide (1 g) which stirred at 120 °C for 1 h to afford the product **81**, respectively. After reaction completion, the isolated yields of both products were obtained by utilizing column chromatography. In which the stationary phase was silica gel, the mobile phase ethyl acetate and petroleum ether in a ratio of 1:3. However, under basic conditions cyclization occurred to give **80**, while in the case of the acidic condition cyclization did not occur and gave **81**.

Mahmoodi et al.[119] described *p*-toluenesulfonic acid promoted regio- and chemoselective synthesis of bispyrimidine derivative, 2,8-dithioxopyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,5(1*H*)-dione **82** through treatment of thiobarbituric acid **11/11b** (1 mmol) and diversified aldehydes **1** (0.5 mmol) in ethanol under reflux (Scheme 59). Aromatic and heteroaromatic aldehydes **1** were reacted well and gave moderate to higher yield. The pure **82** was obtained as an orange powder.

Yadav et al.[120] have used highly diastereoselective and bifunctional catalyst L-proline (20 mol %) to afford single-pot

Scheme 59. *p*-TSA-Mediated Synthesis of 82

1 11/11b 82

Product 82: R_1 = H-, Yield = 72-81 %, Total entry = 4, Time = 260-320 min;
R_1 = Et-, Yield = 78 %, Total Entry = 1, Time = 330 min;
Ar = 4-(OMe)-C_6H_4-, 4-Cl-C_6H_4-, 4-(NO_2)-C_6H_4-, 2-Thiophene-
(**1** = 0.5 mmol, **11/11b** = 1 mmol)

synthesis of 4-(4-chlorophenyl)-5,7-dioxo-1-phenyl-1,4,5,6,7,8-hexahydropyrazolo-[4′,3′:5,6]-pyrano[2,3-*d*]-pyrimidine-3-carboxylate **84** by the four-component equimolar (1 mmol) reaction of **1**, **11**, phenyl hydrazine **28a**, and dimethyl but-2-ynedioate **83** in ethanol as a solvent at 60 °C (Scheme 60). However, without catalyst at RT, the desired product was not obtained. The nature and position of the various groups on an aromatic ring of **1** have not significantly affected the isolated yield of **84**.

3.2.2. Basic Organocatalyzed Synthesis. Organo-based catalysts are dibutyl amine, *N*,*N*-diisopropylethylamine, theophylline, etc. Maghsoodlou et al.[121] afforded **85** catalyzed by sodium acetate (5 mol %) utilizing the reaction of **1** (1 mmol) with **12** (1 mmol) and **11** (1 mmol) at 50 °C in which aqueous ethanol was used as a solvent (Scheme 61). The use of polar solvent gave a higher isolated yield of **85** compared to nonpolar solvents. Product formation also depended mostly on temperature. After the end of reaction, the pure **85** was gained by recrystallization with ethanol. The nature (electronic) and position of various groups on the aromatic ring of **1** did not remarkably affect the isolated yield of **85**.

After that, various groups synthesized derivatives of **86** using single-shot 3-CR of **1**, **11/11a**, and **12** using various catalysts, solvents, and temperatures as shown in Scheme 62 and Table 5 (entries 1−8). It could be seen from the Table 5 that, by changing the reaction conditions, there should be decrease in

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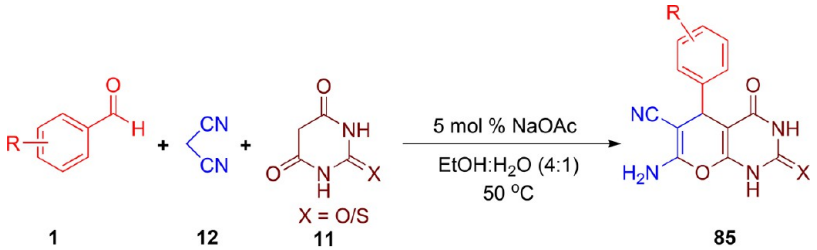
Scheme 60. L-Proline-Mediated Four-Component Reaction to Afford 84

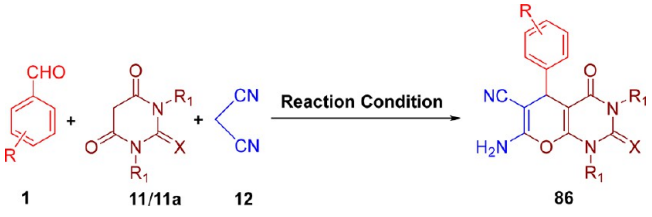
Product 84: Yield = 80-93 %, Total Entry = 17, Time = 2-4 h;
R = 4-Cl-, 3-Cl-, 2-Cl-, 4-Br-, 3-Br-, 2-Br-, 3-F-, 3-(OH)-, 4-(OMe)-, 3-(OMe)-, 4-(OEt)-, H-, 4-Me-, 3-Me-, 4-^{i}Pr-, 4-(NO_2)-, 3-(NO_2)-
(**1** = 1 mmol, **11** = 1 mmol, **28a** = 1 mmol, **83** = 1 mmol)

Scheme 61. Synthesis of 85 Using Sodium Acetate



Product 85: X = O, Yield = 84-95 %, Total Entry = 7, Time = 4-15 min;
X = S, Yield = 94-98 %, Total Entry = 4, Time = 8-28 min;
R = H-, 4-(NO_2)-, 3-(NO_2)-, 2,4-di-Cl-, 4-Cl-, 3-Cl-, 2-Cl-
(**1** = 1 mmol, **12** = 1 mmol, **11** = 1 mmol)

Scheme 62. Synthetic Protocol for 86 (R_1 = -H/-Me) Using Various Basic Organocatalysts



reaction time and the isolated yield of the product are relatively same.

Table 5 shows discrete reaction conditions for preparation of pyrano[2,3-*d*]pyrimidine derivatives from the one-pot 3-CR reaction of aryl aldehyde **1** with barbituric acid/1,3-dimethyl barbituric/thiobarbituric acid (**11**/**11a**) and malononitrile **12**. Here, all of the reactants are taken in equal amount. Different reported basic organocatalysts were covered herein such as dimethyl amine, dibutyl amine, 1,4-diazabicyclo[2.2.2]octane, TMU-16-NH_2, *β*-cyclodextrin, poly(4-vinylpyridine), and theophylline. In all entries, X=O, i.e., barbituric acid. TMU-16-NH_2-promoted reaction gave highest yield among all other basic organocatalysts but it took 1 h. After that, poly(4-vinylpyridine)-catalyzed reaction gave 89−98% yield of **86** in shorter reaction time than others. Reactions reported by Morsali et al.[125] took the longest time to complete the reaction among all other reported reactions showed in Table 5. From entries 1−3, R_1 = H-/Me-, In these three reactions, various EWGs/ERGs on an aromatic ring of aldehyde did not considerably affect the isolated yield of **86**, and for entry 4, R_1 = H-. After reaction completion, the catalyst was recollected and used again without any conseiviable decrease in efficiency for five runs continuously for TMU-16-NH_2 promoted reaction. It was also found that **1** bearing electron-withdrawing substituents were more reactive compared to those bearing electron-releasing substituents. Mohamadpour[126] also obtained analogues of **86** analog using *β*-cyclodextrin catalyst in H_2O at 80 °C (Table 5, entry 6). Mohamadpour[126,128] developed derivatives of **86** (where R_1= -H, -Me) using same substrate scope as shown in Scheme 62 (Table 5, entries 7 and 8), in which the *β*-cyclodextrin-catalyzed reaction gave higher yield by requiring relatively higher time than the theophylline-catalyzed reaction.

Table 5. Various Reaction Conditions for One-Pot 3-CR to Prepare Pyrano[2,3-*d*]pyrimidines 86

entry	reaction condition (catalyst, solvent, temperature)	yield (%)	reaction time	ref
1	dimethyl amine (5 mol %), EtOH, RT	87−93	15−25 min	Rathinam and Appaswami[122]
2	dibutyl amine (20 mol %), aq EtOH, reflux/RT	83−94	53−110 min	Dongre et al.[123]
3	DABCO (10 mol %), aq EtOH (1:1), RT	82−94	30−40 min	Dongre et al.[124]
4	TMU-16-NH_2 (5 mol %), solvent, reflux	84−100	1 h	Morsali et al.[125]
5	*β*-cyclodextrin (10 mol %), H_2O, 80 °C	79−95	10−30 min	Mohamadpour[126]
6	poly(4-vinylpyridine) (24 mg), H_2O, reflux	89−98	5−15 min	Shirini et al.[127]
7	theophylline (10 mol %), aq EtOH, 50 °C	76−89	10−25 min	Mohamadpour[128]

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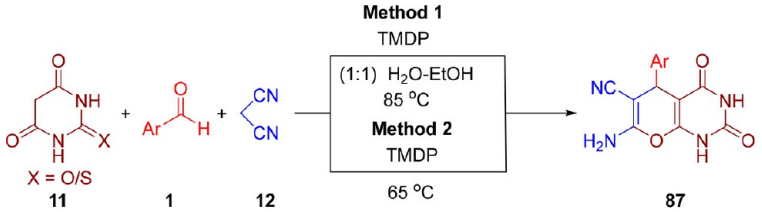
Scheme 63. 4,4′-Trimethylenedipiperidine-Promoted Synthesis of 87

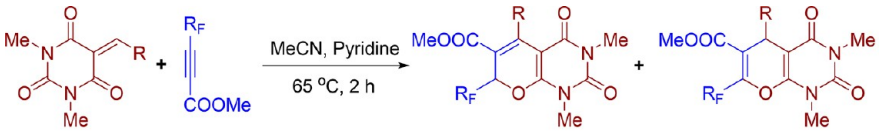


Product 87: **Method 1**, X = O, Yield = 72-88 % , Total Entry = 10, Time = 60 min;
X = S, Yield = 79-87 %, Total Entry = 10, Time = 75-110 min;
Method 2, X = O, Yield = 78-92 %, Total Entry = 10, Time = 30 min;
X = S, Yield = 81-90 %, Total Entry = 10, Time = 35-65 min;
R = 4-Cl-C_6H_4-, C_6H_5-, 3-Cl-C_6H_4-, 2,3-di-Cl-C_6H_3-, 2,4-di-Cl-C_6H_3-, 4-Br-C_6H_4-, 4-(NO_2)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(CF_3)-C_6H_4-, Furan-2-yl-

Scheme 64. Per-6-NH_2-β-Cyclodextrin-Promoted Synthesis of 88

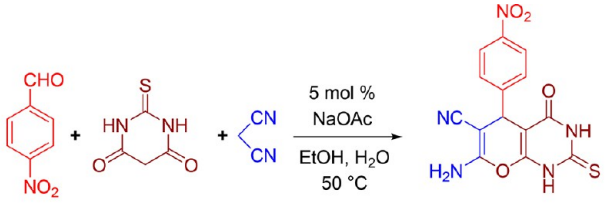
Product 88: R_1 = H-, Yield = 81-94 %, Total Entry = 15, Time = 3-12 min;
R_2 = Me-, Yield = 83-92 %, Total Entry = 5, Time = 5-12 min;
R = H-, 4-F-, 4-Cl-, 2-(OH)-, 4-Br-, 3-(NO_2)-, 2,4-di-Cl-, 2-(OMe)-, 2-Cl-, 4-(OMe)-
2-(NO_2)-, 4-Me-, 4-(NO_2)-, 2,4-di-(OMe)-, 3-(OH)-

Scheme 65. Synthesis of 90/90a Using Acetonitrile-Py at 65 °C



Product 90/90a: R_F = CF_3, Yield = 51-99 %, Total Entry = 11; R_F = -C_2F_5, Yield = 33 %, Total Entry = 1;
R_F = $^nC_3F_7$-, Yield = 30 %, Total Entry = 1;
R = Ph-, 2-Me-Ph-, 3-Me-Ph-, 3-(OMe)-Ph-, 3-Cl-Ph-, 3-Br-Ph-, 4-Me-Ph-, 4-(OMe)-Ph-,
4-Br-Ph-, 4-(CN)-Ph-, 4-F-Ph-

Scheme 66. Synthesis of 91 Using Sodium Acetate



Product 91: Yield = 75-90 %, Total Entry = 5;
Ar = 2-Cl-C_6H_4-, α-Naphthalene-, 2,4-di-(OMe)-C_6H_3-, 4-(NO_2)-C_6H_4-, 2-(OH)-4-(OMe)-C_6H_3-
(**1** = 1 mmol, **11a** = 1 mmol, **12** = 1 mmol, EtOH = 2 mL)

Zaharani et al.[129] synthesized derivatives of **86**, i.e., **87**, using N-heterocycle 4,4′-trimethylenedipiperidine (TMDP) both as a solvent as well as catalyst via the treatment of **11** with discrete **1** and **12** using two methods (Scheme 63). In the first method, the catalyst was used along with the equivalent mixture of water and ethanol, and the mixture was heated at 85 °C. In second method, the catalyst was used alone at 65 °C. It was found that TMDP catalyst was superior than two equivalents of the piperidine ring. Distinctly substituted **1** with either EWG/ERG have no any considerable effect on an isolated product. However, 3-chloro- and 4-trifluoromethane analogues gave lower yield. The recycled catalyst was further used up to five times repeatedly with no any notifiable loss of efficiency. In addition, this reaction taken longer time than entries 1−4 and 6−8 and lower than entry 5 (Table 5).

Mohamadpour[130] derived **88** through the Michael addition reaction followed by Knoevenagel reaction of **1** with **12** and **11/11a** using per-6-NH_2-β-CD as catalyst at RT as shown in

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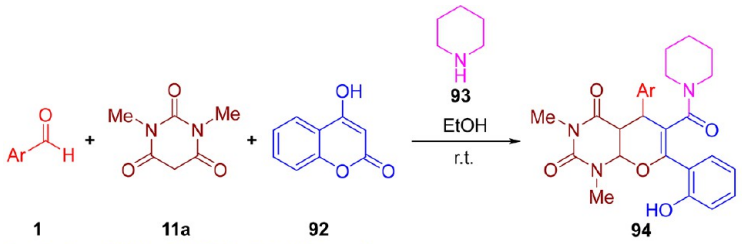
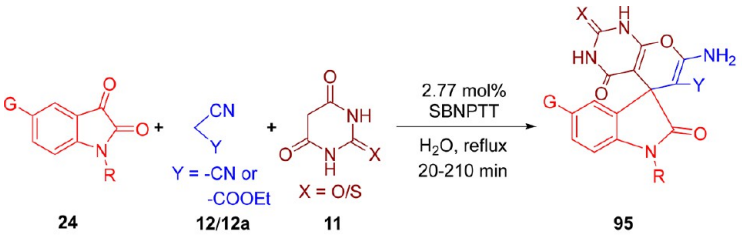
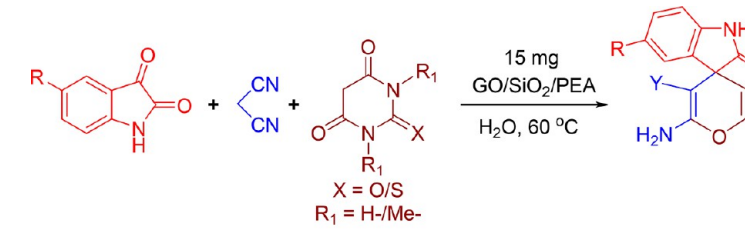
Scheme 67. Green Solvent, EtOH-Promoted Synthesis of 94 Using a Four-Component Reaction



Scheme 68. Silica-Bonded *N*-Propylethylenetetramine-Catalyzed Synthesis of 95



Scheme 69. Graphene Oxide/SiO_2/PEA-Promoted Synthesis of 96 at RT



Scheme 64. Without catalyst, **88** was not formed. The catalyst was separated from the crude product and recycled followed by drying, and was reused with slight efficiency loss up to five runs, and the pure **88** was obtained by recrystallization with ethanol. EWG or ERG on **1** were not affected the isolated yield of **88**. This reaction provides relatively comparable isolated yield with all the entries described in Table 5 and in lower reaction time than all the entries in Table 5.

Xu et al.[131] developed the first diastereoselective, catalyst-free, and highly efficient synthetic cascade routes for perfluoroalkylated **90**/**90a**. They used a three-component reaction of 5-arylidenebarbituric acids **89** methyl perfluoroalk-2-ynoates **83a**/**83b** and pyridine derivatives in the presence of acetonitrile as solvent at 65 °C to achieve the major product **90** (Scheme 65). **1** with either ERGs/EWGs was treated efficiently and resulted in the normal optimal isolated yield of **90**. The other substituents, i.e., alkyl/cyclohexyl group on alkeledine group of barbituric acid, did not give the reaction.

The same reaction conditions was utilized by Habibi-Khorassani et al.[132] This group of co-workers reported kinetic and mechanistic studies on the one-pot synthesis of 7-amino-5-(4-nitrophenyl)-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano-[2,3-*d*]-pyrimidine-6-carbonitrile **91** (Scheme 66). They used equimolar (1 mmol) reaction of **1** with **12** and **11** in sodium acetate with aqueous ethanol at 50 °C. In this method, UV−visible spectrophotometry apparatus was used to monitor the mechanism and kinetics of the presented protocol. This reaction consisted of three main steps in which first step was identified as the slowest step (rds) with second-order. When solvents with a high dielectric constant were used then the rate of all reactions got increased which could be related to differences in stability of reactants and activated complex by the solvent in its transition state. Also, with increasing temperature also rate of reaction got increased. They also used zinc acetate as a catalyst different from sodium acetate resulted in decreased reaction rate and this was due to more interaction between Zn^{2+} ion compared to Na^{+} ion.

Irani et al.[133] used a four-component reaction of **1** with **11a**, **92**, and **93** in ethanol as a solvent at room temperature to afford **94** (Scheme 67). **1** with electron-releasing substituents gave higher isolated yield of **94** compared to electron-withdrawing substituents carrying aryl aldehyde **1**. However, naphthaldehyde gave a higher isolated yield of **94**.

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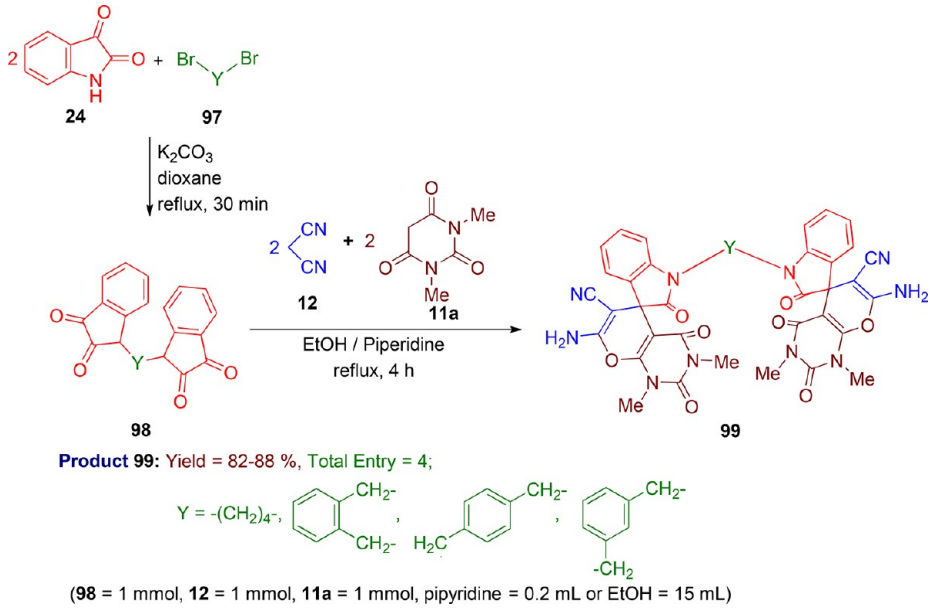
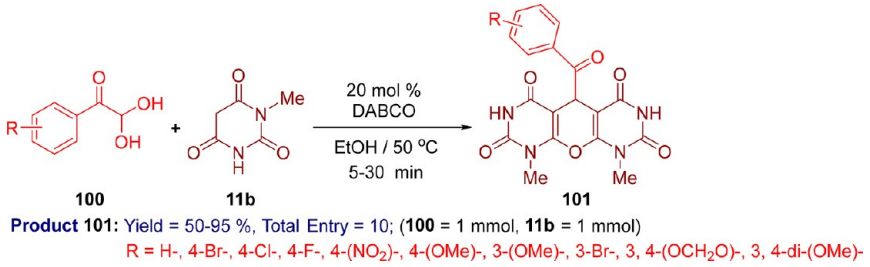
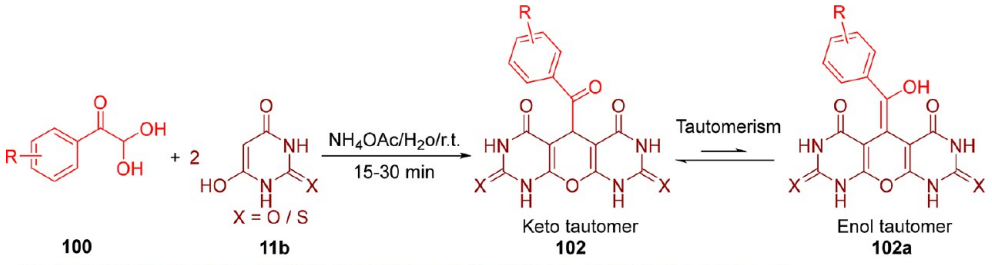
Scheme 70. Synthesis of 99 through Two Steps: (i) K_2CO_3, Dioxane; (ii) EtOH/Piperidine



Scheme 71. DABCO-Promoted Synthesis of 101



Scheme 72. Synthesis of 102 in Ammonium Acetate with Water



Niknam and Abolpour[134] derived spiropyrano derivatives **95** catalyzded by solid base, silica-bonded *N*-propyltriethylenetetramine (2.77 mol %) one-shot procedure via 3-CR of **24** (1 mmol) with **12**/**12a** (1 mmol) and **11** (1 mmol) in water as green solvent under reflux (Scheme 68). After reaction completeness, the catalyst was recollected and used again four times without any loss of efficiency. Malononitrile **12** reacted at faster rate than ethyl cyanoacetate **12a** and this might be because of lower reactivity of cyanoacetates. Various EWG/ERG substitution on **1**'s ring did not affect the isolated yield of **95** except for its F analogues which gave only 67% yield with thiobarbituric acid.

Toorbaf and Moradi[135] also devised spiropyranopyrimidine **96** by using GO-functionalized 2-(1-piperazinylethylamine) (GO/SiO_2/PEA, 15 mg) as a solid base promoter using Hummers' method to synthesize spiropyranopyrimidinediones **96** through treatment of **24** (1 mmol) with **12** (1 mmol) and **11**/**11a** (1 mmol) in water at 60 °C (Scheme 69). At the end, precipitate was dissolved in ethanol, catalyst was separated via filtration. Ethanol was utilized to recrystallize the crude product. The catalyst was used further five runs without conceivable efficiency loss. The substitution on **1** did not affect the isolated yield of **96**. This reaction was completed in shortest reaction time than the previous one.

Ghozlan and co-workers[136] synthesized **99** (Scheme 70) through two steps. The first step involved the treatment of isatin with dibromo derivatives in the presence of K_2CO_3, a base in dioxane under reflux of 30 min to afford corresponding

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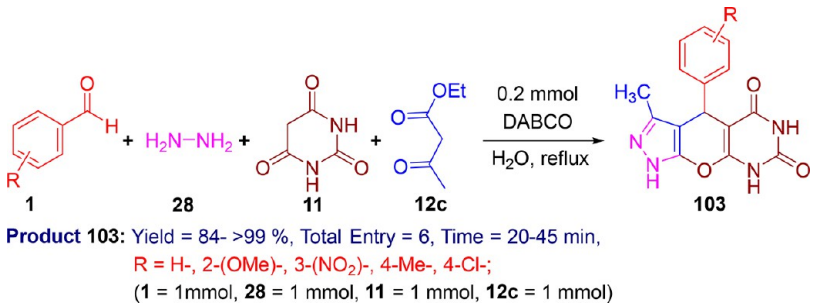
Scheme 73. Four-Component Synthesis of 103 Using DABCO



Scheme 74. Synthetic Approach to Prepare Derivatives of 104 under Various Reaction Conditions

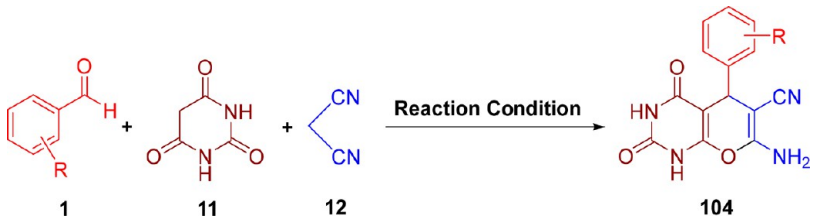


Table 6. Diversified Synthetic Approaches for Analogues of 104 Using Miscellaneous Organocatalysts

entry	reaction condition (catalyst, solvent, temperature)	yield (%)	reaction time (min)	ref
1	TBAB (12 mol %), water, reflux	80–90	30–45	Mobinikhaledi and Farad[140]
2	verjuice (10 mmol), oil bath, reflux	86–95	20–42	Shirini[141]
3	ethylene glycol (3 mL), oil bath, 100 °C	78–94	80–115	Mohamadpour[142]
4	taurine/ChCl DESs (80 mg), H_2O, 90 °C	88–94	19–35	Shirini et al.[143]
5	DES (ChCl-urea-thiourea, 36 mol %), H_2O, reflux	88–94	15–27	Shirini et al.[144]
6	[Ch]Cl:Gab (10 mol %), solvent-free, 75 °C	87–94	8–23	Shirini et al.[145]
7	concentrated kiwi juice (24 mg), EtOH, RT	85–98	30–65	Marandi et al.[146]
8	vitamin B_{12} (7.35×10^{-5} mol %), aq EtOH (1:1), 60 °C	79–97	10–30	Marandi et al.[147]

bis-isatin derivatives **98**. The reaction of bis-isatin **98** (1 mmol) with **12** (1 mmol) and **11a** (1 mmol) in absolute alcohol (15 mL) or piperidine (0.2 mL) as catalyst under reflux of 4 h afforded **99**. As the reaction was completed, the crude product **99** was recrystallized with ethanol or dioxane.

Rimaz et al.[137] synthesized symmetric 5-aryloyl-1,9-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*′]-dipyrimidine-2,4,6,8(1*H*, 3*H*,7*H*)-tetraone **101** regio- and chemoselectively through a treatment of arylglyoxalmonohydrate **100** (1 mmol) with **11b** (1 mmol) using DABCO (20 mol %) as a catalyst in ethanol as a solvent at 50 °C (Scheme 71). EWGs on **100** gave a higher yield of **101** compared to that with ERGs. 4-Bromo and 4-chloro analogues gave 60% yield only.

Rimaz et al.[138] reported a highly regio-chemoselective synthesis of pyrano[2,3-d:6,5-*d*′]dipyrimidine-2,4,6,8-(3*H*,5*H*,7*H*,9*H*)-tetraones **102** and its sulfur analogue by reacting **100** (1 mmol) with **12** (2 mmol) in excess ammonium acetate (5 mmol) and water at RT (Scheme 72). Only in 4-Cl and 4-F analogues of **102** undergo keto−enol tautomerism in DMSO-d_6 solution, but the leading tautomer was keto only.

Heravi et al.[139] described a one-pot four-component protocol for fused tricyclic pyrazolopyrano[2,3-*d*]-pyrimidine-diones **103** by reacting **1** (1 mmol), **28** (1 mmol), **11** (1 mmol), and **12c** (1 mmol) in the presence of DABCO (0.2 mmol) as a catalyst under reflux for 20−45 min (Scheme 73). It was observed that, due to hydrogen bonding with the substrates, they used polar protic solvents to attain the higher yield of **103**.

3.2.3. Miscellaneous Organic Catalyst-Based Synthesis. Mobinikhaledi and Farad[140] utilized TBAB (10 mol %) as an efficient catalyst to synthesize **104** by treating **1** (1 mmol) with **11** (1 mmol) and **12** (1 mmol) in water under reflux (Scheme 74). After completion of reaction, the combined reaction mixture was cooled in fridge to get the crude **104** which then recrystallized with aqueous ethanol. The yield of **104** remain unaffected by the nature and position of various substituents on **101** (Table 6, entry 1). Thereafter, discrete researchers came and gave the synthetic approaches for **104** using the same substrate scope, i.e., **1**, **11**, and **12** (Scheme 74).

Table 6 shows different reaction conditions for the production of pyrano[2,3-*d*]pyrimidine scaffold **104** via the single-shot three-component treatment of aryl aldehyde **1**, barbituric/thiobarbituric acid **11** and an active methylene containing malononitrile **12**. In which each of the reactants were taken in equimolar amount. Various miscellaneous organocatalysts such as alum, verjuice, ethylene glycol, Taurine/ChCl DESs, ChCl-Urea-thiourea DESs, [Ch]Cl:Gab, Concentrated Kiwi juice and vitamin B_{12} were reported were included for the preparation of **104**. In this table, entries 2 and 4−6 derived barbituric acid as well as 2-thiobarbituric acid derivatives of **104**, while in all other entries, only the barbituric acid derivative of **104** were gained. In all of these reactions, relative similar isolated yield of **104** were obtained. Out of which comparatively higher yield were obtained in shorter reaction time when vitamin B_{12} used as catalyst. Ethylene-glycol-catalyzed reaction takes longer time requiring 100 °C

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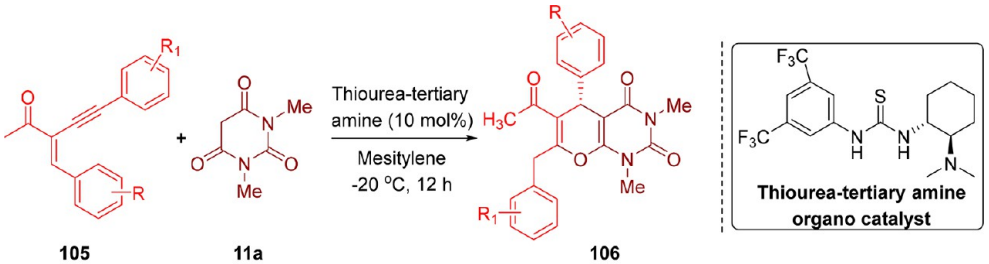
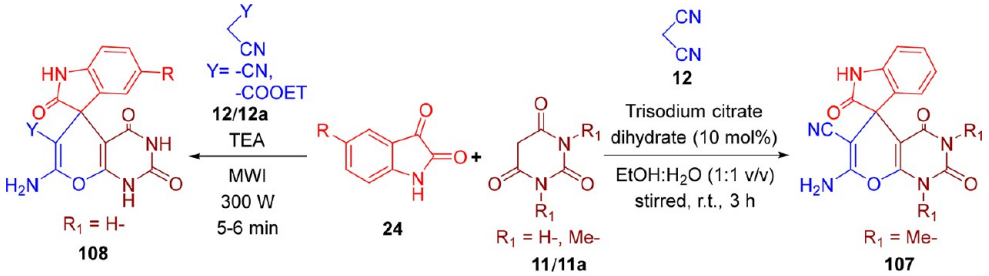
Scheme 75. Thiourea Tertiary Amine, an Organocatalyzed Synthesis of 106



105 11a 106

Product 106: Yield = 34-84 %, Enantiomeric excess = 61-94 %, Total Entry = 18;
R = 2-(OMe)-, 3-(OMe)-, 4-Me-, 4-Br-, 3-Br-, 4-Cl-, 2,4-di-Cl-, 4-F-, 4-(NO_2)-, biphenyl-, H-;
β-naphthaldehyde, cyclohexyl-; R_1 = H-, 4-Cl-, 4-Br-, 4-F-, 2-Me--, 3-Me-, 4-Me-
(**105** = 0.12 mmol, **11a** = 0.1 mmol)

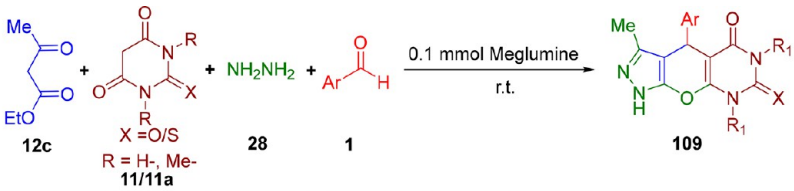
Scheme 76. Synthesis of 107 and 108 by Utilizing Trisodium Citrate Dihydrate and TEA Catalysts



R_1 = H- (108) 24 R_1 = H-, Me- (11/11a) R_1 = Me- (107)

Product 107: **24** = 1 mmol, **11a** = 1 mmol, **12** = 1.1 mmol
Product 108: Yield = 72-87 %, Total Entry = 8; R = H-, Br- (each reactant is equimolar)

Scheme 77. Meglumine-Promoted Synthesis of 109 at RT



12c X =O/S R = H-, Me- (11/11a) 28 1 109

Product 109: X = O, R_1= H-, Yield = 83-95 %, Total Entry = 34, Time = 15-360 min;
R_1 = Me-, Yield = 91-95 %, Total Entry = 3, Time = 30-60 min;
X = S, R_1= H-, Yield = 32-95 %, Total Entry = 2, Time = 15-20 min;
(**12c** = 1 mmol, **11/11a** = 1 mmol, **28** = 1 mmol, **1** = 1 mmol)
Ar = C_6H_5-, 3-(NO_2)-C_6H_4-, 4-Me-C_6H_4-, 4-Cl-C_6H_4-, 2-(OMe)-C_6H_4-, 3-(OMe)-C_6H_4-, 3,4-di-(OMe)-C_6H_3-, 2,3,4-tri-(OMe)-C_6H_2-, 3-(PhO)-C_6H_4-, 2-(OH)-4-(OMe)-C_6H_3-, 3-(OMe)-4-(OH)-C_8H_3-, 2-Cl-C_6H_4-, 2-(OEt)-4-(OH)-C_8H_3-, 2-(OMe)-5-(^{i}Pr)-C_6H_3-, 4-(CMe_3)-C_6H_4-, 2-F-C_6H_4-, 3-F-C_6H_4-, 4-F-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2,4-di-Cl-C_6H_3-, 2-Br-C_6H_4-, 3-Br-C_6H_4-, 4-Br-C_6H_4-, 2-(OH)-5-Br-C_6H_3-, 2-(NO_2)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NO_2)-C_6H_4-, 2-(OH)-5-(NO_2)-C_6H_3-, 3-(NO_2)-4-(OH)-C_6H_3-, 3-(CF_3)-C_6H_4-, 4-(CF_3)-C_6H_4, 4-(COOH)-C_6H_4-, Thiophene-2-yl-, 2-pyridyl-, 1-naphthyl-

temperature compared to other reaction conditions of Table 6 (entries 1, 2, and 4−8). Also, in all of these reactions, the electronic nature of various EWGs/ERGs on an aromatic ring of aryl aldehydes were not affected the isolated yield of the product **104** to any measurable way.

Yan et al.[148] used thiourea tertiary amine as a bifunctional organocatalyst (10 mol %) and reported the synthesis of chiral **106** with good enantiomeric excess (61−94%) through asymmetric [3+3] annulation treatment of 2-(1-alkynyl)-2-alken-1-ones **105** (0.12 mmol) and **11a** (0.1 mmol) in mesitylene at −20 °C under a nitrogen atmosphere (Scheme 75). After termination of reaction, column chromatography used to purify the mixture with dichloromethane/ethyl acetate used as an eluent. **105** with ERG gave a higher isolated yield of **106** than EWG, and biphenyl-aldehyde and β-naphthaldehyde also gave higher yield. The large steric hindrance ambiguously affected the yield and enantioselectivity but the increased polarity of the substrate was in favor. Maximum enetiomeric excess(ee) was found when R_1= 4-Cl- and R= -H derivative, i.e., 94% and lowest for R_1 = -H and R = 4-Cl- derivative, i.e., 61%.

Sharma et al.[149] reported the environmentally friendly synthesis of 7′-amino-1′,3′-dimethyl-2,2′,4′-trioxo-1′,2′,3′,4′,4a′,8a′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-*d*]-pyrimidine]-6′-carbonitrile **107** via equimolar reaction of **24**, **12**, and **11a** using trisodium citrate dihydrate (10 mol %) in aqueous ethanol which was then stirred for 3 h at RT (Scheme 76). However, the method did not required any chromatographic technique for recrystallization. This group also studied molecular modeling, spectroscopic investigations, and computational studies by using DMSO solvate. Mahmoud and coworkers[150] reported a green microwave-assisted single-pot synthesis of novel analogues of spiropyranopyrimidine **107**, i.e., **108** (Scheme 76). For this purpose, they used a three-

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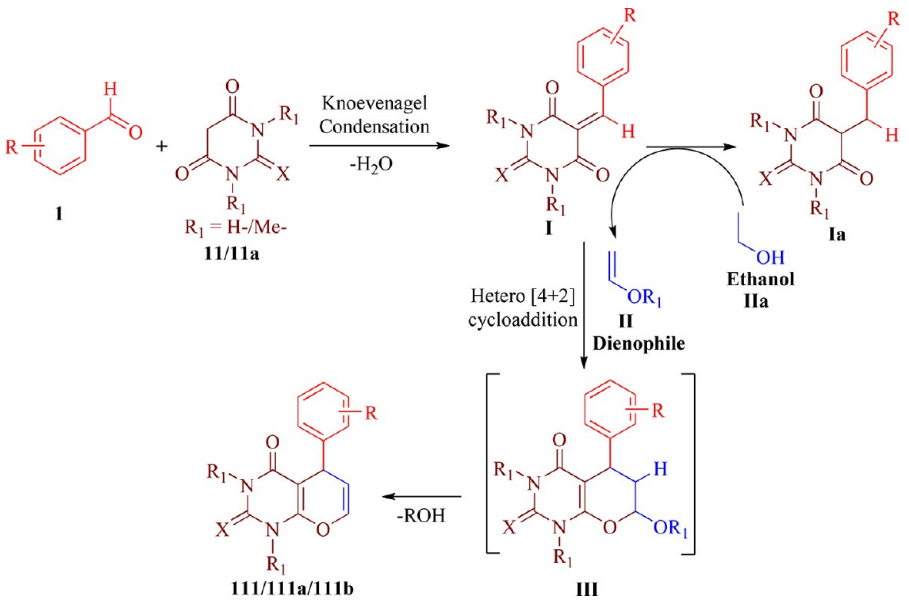
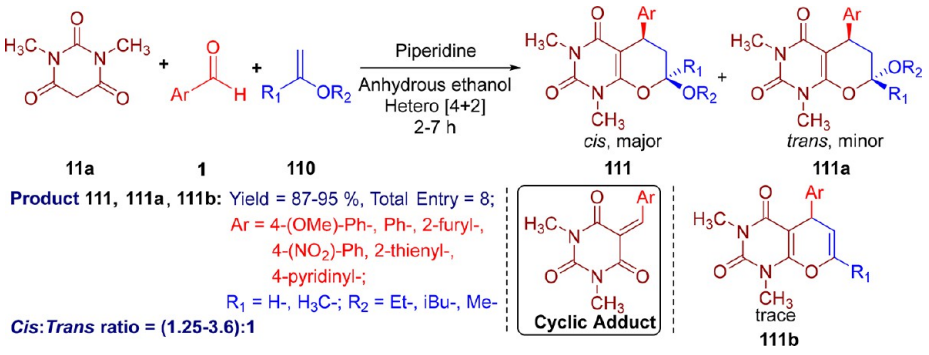
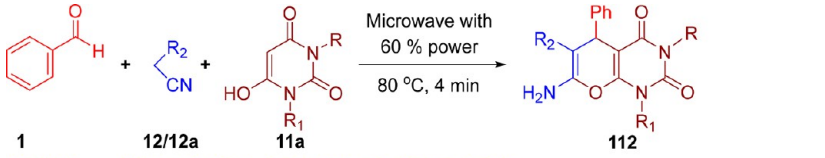


Figure 13. Possible mechanism to synthesize novel derivatives of **TS-2** using domino Knoevenagel/HDA.

Scheme 78. Piperidine-Promoted Synthesis of 111, 111a, and 111b



Scheme 79. Synthesizing 112 under Microwave Irradiation



component reaction of **24** with **12/12a** and **11** using triethylamine (TEA) under MWI to afford **108** under neat or solvent-free condition. This reaction gaves higher yield in shorter reaction time than previous synthetic protocol.

Li et al.[151] devised pyrazolopyranopyrimidine derivatives **109** by treating equimolar amounts of **12c**, **11/11a**, **28**, and **1** utilizing meglumin (0.01 mmol) as catalyst in water at RT (Scheme 77). A variety of **1** possessing either ERGs/EWGs did not affect the final yield of **109**. Other heteryl aldehydes also reacted well and gave higher yield.

3.2.4. Organocatalyzed Synthesis Involving Domino Hetero-Diels–Alder Reaction. The synthesis of analogues of **TS-2** through the hetero-Diels–Alder (HDA) reaction which involved the formation of Knoevenagel adduct diene through a condensation of barbituric acid with distinct aryl aldehydes then underwent the HDA reaction with a dienophile to give the desired product. A common proposed mechanism for domino Knoevenagel/HDA reaction is shown in Figure 13. First, the Knoevenagel condensation of distinctly substituted aromatic aldehydes **1** with **11/11a** afforded 5-benzylidinebarbituric acid **I**. The exocyclic double bond of **II** was readily oxidized ethanol **IIa** to acetaldehyde which acts as a dienophile in its enol form **II** for further reaction, and the adduct **I** gave **Ia** by reduction of the double bond. Now, the domino HDA reaction of the adduct **I** and vinyl ether **II** afforded the intermediate **III** which on removal of ethanol gave the expected pyrano[2,3-*d*]pyrimidinedione **111/111a/111b**.

Palasz[152] synthesized **111** [*cis*:*trans* ratio of (1.25−3.6):1] via treatment of **11a**, **1**, and **110** in piperidine and anhydrous ethanol (Scheme 78). The position and nature of different substituents on the aromatic ring of **1** did not remarkably affect

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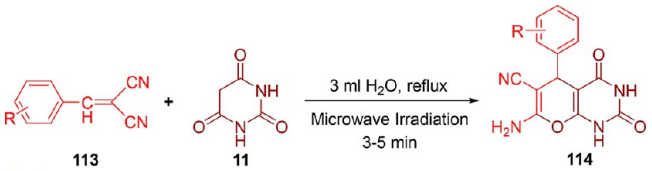
the isolated yield of **111**/**111a**/**111b**. The *cis*-isomer was formed as the major product.

3.2.5. Organocatalyzed Synthesis Involving Microwave Irradiation. Devi et al.[153] demonstrated single-pot, 3-CR in the solid state of **1** (1 mmol), alkyl nitriles **12**/**12a** (1 mmol), and **11a** (1 mmol) under MWI (60% power) at 80 °C to afford **112** (Scheme 79). Using DMF as solvent, the reaction was completed in 10−12 min and dimethylformamide with Et_3N produced a 60−70% isolated yield of **112**. Also with or without triethylamine catalyst, the reaction was completed in 4−8 min and produced 70−90% and 70−95% yield of **112**, respectively.

To attain the same derivatives of **112**, Gao et al.[154] effectively synthesized 7-amino-6-cyano-5-aryl-5*H*-pyrano[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-diones, **114** through two-component reaction of arylidene malononitrile **113** (1 mmol) and **11** (1 mmol) in water under MWI (Scheme 80). The reaction was

Scheme 80. Microwave-Irradiated Synthesis of 114 in Water



completed just in 3−5 min. Different EWGs/ERGs on aryl ring of arylidene malononitrile **113** did not affect the overall yield of **114**. Both of these reactions gave comparatively similar yield in a shorter reaction time.

Avvadukkam et al.[155] used macrocyclic *β*-CD as the solid-phase catalyst in the solvent-free synthesis of pyrano[2,3-*d*:6,5-*d*′]dipyrimidine **115** through a reaction of **1** with 2,2-dimethyl-1,3-dioxane-4,6-dione **60** and 6-amino-1,3-dimethyluracil **77** under MWI (Scheme 81). After termination, **115** was separated from reaction mixture, and the catalyst obtained was then washed with ethanol, filtered, dried under reduced pressure and reutilized three runs without significant loss of. Also, **115** was purified, recrystallized using ethanol and their single crystal was obtained followed by slow evaporation in a mixture of DMF and water. The reaction proceeded with solid aryl aldehydes only while in case of aliphatic and liquid aromatic aldehydes, there was no product formation and with bulky fused aldehydes, product was formed in trace amount only with a slow rate.

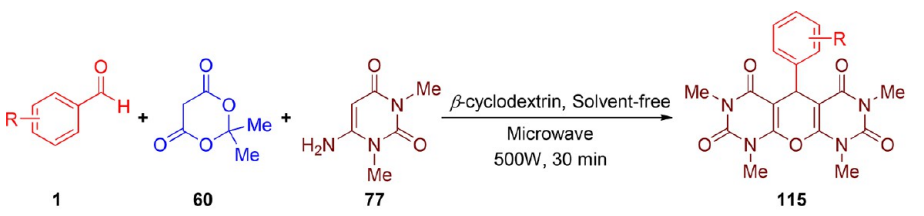
3.2.6. Organocatalyzed Reaction Using Electrolysis. By using electrolysis method, Kazemi-Rad et al.[156] synthesized chrominopyrano[2,3-*d*]-pyrimidinediones **116** and **117** by the equimolar reaction of 4-hydroxycoumarin **92**, **11**, and diversified **1** or **24** in acetonitrile in the presence of tetrabutyl ammonium fluoride (TBAF) (Scheme 82). The use of Pt electrode as anode and iron electrode as cathode at a constant density of the current, 4 $mAcm^{-2}$ with the electricity of 0.12 $Fmol^{-1}$. However, by using higher amount of current density, the yield of desired product got decreased. Before electrolysis the formation of brown solution indicated that the reaction was started. EWGs on an aromatic ring of **1** gave higher yield than those with ERGs. Also, isatin **24** was reacted well instead of aldehydes but gave lower yield than aldehydes. In both of these reactions carried out using electrolysis method involved insitu generation of base.

Instead of this reaction protocol, Veisi et al.[157] reported a highly efficient pathway to synthesize cyano/ethyl-7-amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]-pyrimidine-6-carbonitrile **118** or **119** by utilizing one-pot electro-organic equimolar (1 mmol) reaction of **1**, **11**, and **12** or **12a** in an undivided cell at 40 °C in ethanol using the constant density of the current of 0.01 A cm^{-2} (i.e., I = 50 mA and electrode surface = 5 cm^2) in tetrabutylammonium perchlorate (TBAP) as electrolyte (Scheme 83). The undivided cell used here was consisted of cathode (iron electrode) and anode (graphite electrode). The electronic nature and the position of either EWG or ERG on **1** did not affect the isolated yield of **118** or **119**. This reaction gave higher isolated yield of product compared to the previous one.

The mechanism followed in synthesis of a novel scaffolds of pyrano[2,3-*d*]pyrimidine derivative **TS-2** using electrolysis method is shown in Figure 14, in which, at the anode, by the removal of hydrogen gas, an ethoxide ion was formed. Consecutively in the solution, the proton on active methylene group got abstracted by the ethoxide ion to form the malononitrile **12** to form anion **12a**. Now, **12a** attacked the carbonyl carbon of **1** to form **I**, which on the removal of hydroxide ion forms **II**. Now, the active methylene group of **11** attacked by **II** to get **III**, which upon cyclization gave the desired product pyrano[2,3-*d*]pyrimidinedione derivative (**TS-2**).

3.2.7. Organocatalyzed Synthesis Involving Ultrasound Irradiation. Akolkar et al.[158] utilized a supramolecular *β*-CD (20 mol %) as biomimetic catalyst in order to synthesized **120** scaffold through the four-component equimolar (1 mmol) reaction between **12c**, **1**, **11**/**11a**, and **28** in water at 50 °C under ultrasound irradiation at 50 °C (Scheme 84). The crude **120** was then recrystallized from alcohol. A polyBCMO dendritic polymer functionalized by porphyrin-initiated amine was utilized as catalyst (0.3 mol %) by Govindan and co-workers[159] to achieve **121** through treatment of **1** with **12c**, **28** and **11a** under sonication for 15 min (Scheme 84). The precipitated **121** was then filtered and dried to get the pure

Scheme 81. *β*-Cyclodextrin-Promoted Synthesis of 115 Using Microwave Irradiation



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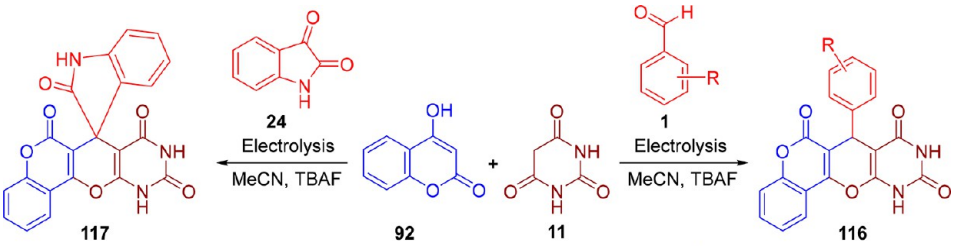
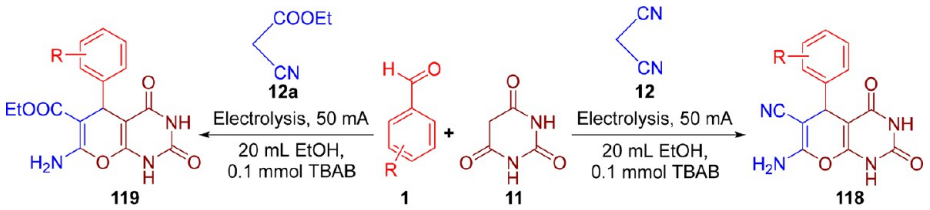
Scheme 82. Use of Electrolysis Method to Synthesize 116 and 117 in the Presence of TBAF



Product 116: Yield = 71-94 %, Total Entry = 7, Electricity passed = 0.06-0.28 F mol^{-1}, Time = 10-45 min;
R = 3-(NO_2)-, 4-(NO_2)-, 2-Cl-, 4-Cl-, 3-Br-, 4-Br-, H-;
Product 117: Yield = 62 %, Total Entry = 1, Electricity passed = 0.37 F mol^{-1}, Time = 60 min;
Isatin
(each reactant taken in equimolar)

Scheme 83. Synthesizing 118 and 119 in the Presence of Tetrabutylammonium Perchlorate



Product 118: Yield = 92-96 %, Total Entry = 8; **Product 119:** Yield = 96-98 %, Total Entry = 8;
R = H-, 4-(OMe)-, 4-Me-, 4-(NO_2)-, 4-Cl-, 4-(NMe_2)-, 3-(NO_2)-, 2-Cl-; (Each reactant = equimolar)

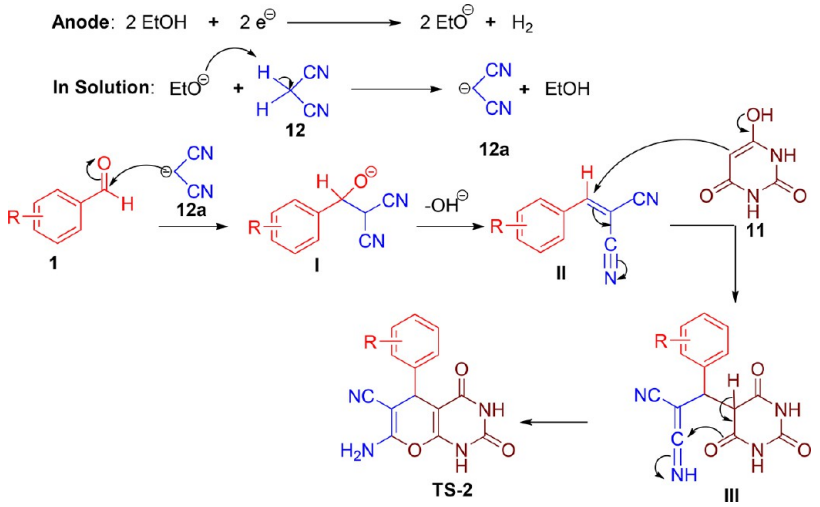


Figure 14. Suggested mechanism for synthesizing 5-aryl-substituted pyrano[2,3-*d*]pyrimidinediones (triones) using the electrolysis method.

121. After end of the process, the promoter was recovered and used again for next 6 runs. The overall yields of **120** and **121** were not affected by various substituents on an aromatic ring of **1**. In the case of the *β*-CD-catalyzed reaction, **1** with ERGs gave lower yield than those with EWGs. In both of the reactions, the catalyst was reused for next 5 and 6 time without significant loss of its catalytic activity. However, polyBCMO dendritic polymer catalyzed reaction gave higher isolated yield of the product **121** in shorter reaction time than *β*-CD.

In 2022, Badiger et al.[160] afforded pyrano[2,3-*d*]-pyrimidinetrione derivative **122** followed by the treatment of **1** (1 mmol) with **11** (1 mmol) and Meldrum's acid **60** (1 mmol) by use of agro-wastewater extract lemon fruit shell ash (WELFSA, 4 mL) as green catalyst in ethanol at RT under ultrasonic irradiation (USI) (Scheme 85). Now, the resultant mixture was diluted with water, filtered, washed and finally pure **122** was recrystallized from ethanol. With aliphatic aldehydes, there was no reaction. However, **1** containing electron-releasing groups showed higher rate than electron-withdrawing substituents. Also, when steric hindrance was close to reaction center, the reactivity of an aromatic aldehyde got decreased. The most advantageous matter of this protocol is that, the catalyst can be made from agro-waste.

3.2.8. Organocatalysis Involving Visible Light Irradiation. Ibad et al.[161] reported a novel and green synthetic route to afford tetrahydro-1*H*-pyrano[2,3-*d*]-pyrimidine **123** by hetero-cyclization through Knoevenagel condensation of 2-thiobarbituric acid **11a** (2 mmol) and **1** (2 mmol) to form cyclic adduct 5-arylidine thiobarbituric acid which then undergo [4+2] cycloaddition with internal alkynes' derivatives **83**/**83b**/**83c**/**83d**/**83e** (2 mmol) in the presence of ethylene glycol acting as a catalyst as well as solvent under visible blue-LED light

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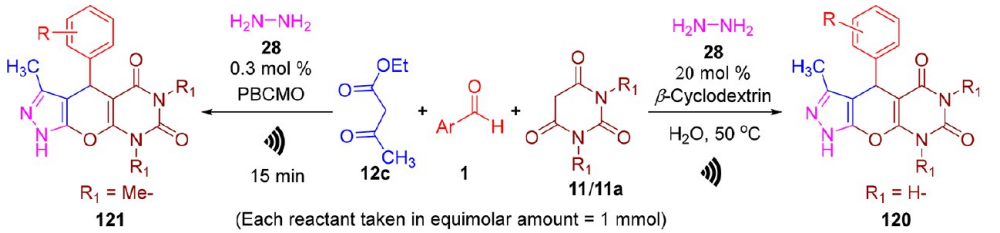
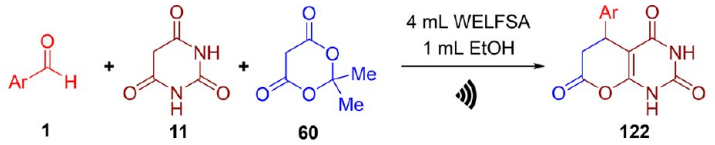
Scheme 84. Ultrasound-Assisted Synthesis of 120 and 121 through Macrocyclic β-CD



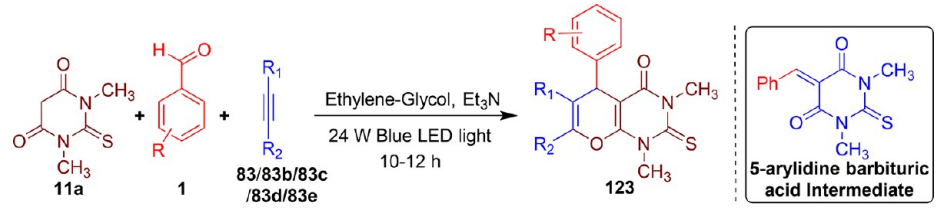
Product 120: Yield = 84-93 %, Total Entry = 21, Time = 25-70 min;
R = C_6H_5-, 2-Cl-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4, 2-(NO_2)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NO_2)-C_6H_4-, 4-Ph-C_6H_4, 4-Br-C_6H_4-,4-F-C_6H_4-, 2-Me-C_6H_4-, 4-Me-C_6H_4-, 2-(OMe)-C_6H_4-, 4-(OMe)-C_6H_4-, 2-(OH)-C_6H_4-, 3,4,5-tri-(OMe)-C_6H_2-, 3-(OH)-4-(OMe)-C_6H_3-, 3-(OH)-C_6H_4-, 4-(OH)-C_6H_4-, 2-Thiophene-, Furan-2-yl-;
Product 121: Yield = 92-99 %, Total Entry = 12; Time = 15 min;
R = C_6H_5-, 4-Br-C_6H_4-, Naphthyl-, 4-Cl-C_6H_4-, 4-(NO_2)-C_6H_4-, 3,4,5-tri-(OMe)-C_6H_2-, 4-(NMe_2)-C_6H_4-, Furan-2-yl-, 4-(OMe)-C_6H_4-, Thiophene-2-yl-, cinnamaldehyde, anthraldehyde

Scheme 85. WELFSA-Promoted Synthesis of 122 Using Ultrasound Irradiation



Product 122: Yield = 80-91 %, Total Entry = 18, Time = 40 min; (**1** = 1mmol, **11** = 1mmol, **60** = 1 mmol)
Ar = C_6H_5-, 3-Cl-C_6H_4-, 4-Me-C_6H_4-, 4-(OMe)-C_6H_4-, 4-Cl-C_6H_4-, 4-F-C_6H_4-, Furan-2-yl-, 4-(NO_2)-C_6H_5-, 3,4-di-(OMe)-C_6H_3-, 2,4-di-(OMe)-C_6H_3-, 2-Cl-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NMe_2)-C_6H_4-, 4-(OH)-C_6H_4-
2-(OH)-3-Quinolinyl-, , 4-(OH)-3(OMe)-C_6H_3-, 3,4,5-tri-(OMe)-C_6H_2-, 2,4-di-(OMe)-C_6H_4-

Scheme 86. Use of 24 W Blue LED Light to Afford 123



Product 123: R_1 = R_2 = -COOEt, Yield = 84-94 %, Total Entry = 12;
R_1 = -COOMe, R_2 = -COOEt, Yield = 86 %, Total Entry = 1;
R_1 = R_2 = -COOMe, Yield = 86 %, Total Entry = 1;
R_1 = -CN or $-NH_2$ or -H, R_2 = -H or Ph-, Yield = 74-87 %, Total Entry = 3;
R = 4-Cl-, H-, 3-(NO_2)-, 4-Br-, 4-(OH)-, 3-(OH)-, 4-Me-, 4-(OMe)-, 2,4-di-(OMe)-, 4-(NO_2)-
(**11a** = 2 mmol, **1** = 2 mmol, **83/83b/83c/83d/83e** = 2 mmol)

irradiation (24 W) (Scheme 86). **1** carrying electron-releasing substituents gave higher yields of **123** in lower reaction time than those carrying electron-withdrawing substituents and also symmetrical alkynes produced a higher yield of the product than asymmetrical alkynes. The more beneficial characteristics of this protocol is the reusability of the ethylene glycol catalyst, i.e., 11 times.

The probable reaction mechanism to afford pyrano[2,3-*d*]pyrimidinedione scaffold using Blue-LED irradiation is shown in Figure 15. Under blue-light irradiation, the most acidic proton of **11a** was removed to generate the radical to form **I**. The carbonyl carbon of an aromatic aldehyde **1** then attacked by **I** to get **III** which upon dehydration via Knoevenagel condensation to form the intermediate **IV**. Now, this glycol-activated intermediate **IV** with acetylene **V**'s derivatives underwent [4+2] cycloaddition to give the desired **123**.

Mohamadpour[162] utilized a single-pot environmentally friendly protocol to afford **124** using a equimolar amount (1 mmol) in a 3-CR of **1**, **12**, and **11**/**11a** in the absence of the catalyst and solvent under visible light irradiation(VLI) (Scheme 87). Usually, for source of visible light, compact fluorescent light (CFLs) (22 W) and light-emitting diodes (LEDs) were used. The presence of various substituents and their electronic nature on **1** did not alter the yield of the **124**. But halogen-substituted **1** gave slightly lower yield than others.

The probable mechanism to synthesize **124** white CFL light is shown in the Figure 16. In the presence of visible light irradiation, an active methylene group of malononitrile **30** gets activated to get **I**. The carbonyl carbon of aromatic aldehyde **1** got attacked by **I** which results in the in situ generation of radical intermediate ylidenemalononitrile **II**, i.e., cyano-olefin followed by Knoevenagel condensation reaction. The intermediate **II** then absorbs hydrogen from methylene of malononitrile and forms radical malononitrile that absorbs hydrogen from the hydroxyl group of enol form of barbituric acid **III** and transformed it to intermediate **IIIa**. The Michael acceptor intermediate **IV** get attacked by intermediate **IIIa** to

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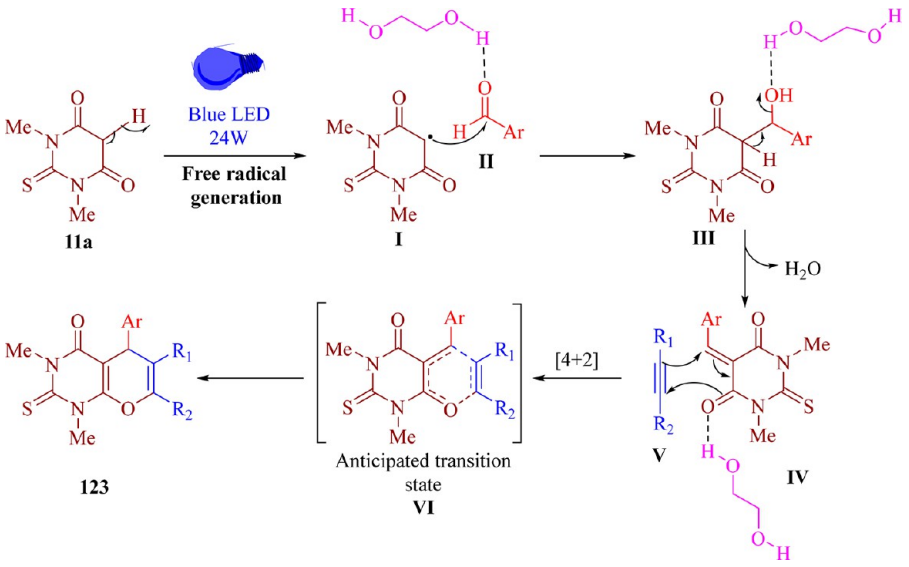
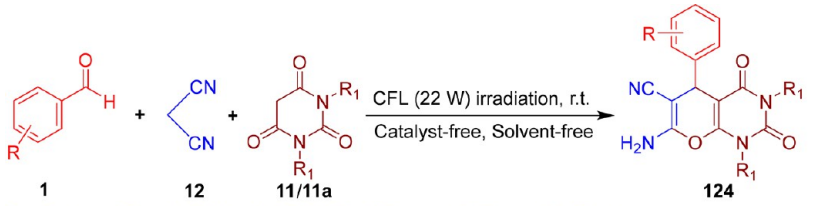


Figure 15. Proposed mechanism to pyranopyrimidinediones under blue LED light irradiation.

Scheme 87. Use of White CFL Light (22 W) to Synthesize 124 in the Absence of Solvent and Catalyst



Product 124: R_1 = H, Yield = 81-95 %, Total Entry = 15, Time = 20-35 min;
R_1 = -Me, Yield = 84-93 %, Total Entry = 4, Time = 25-35 min;
R = H-, 4-Br-,4-(OMe)-, 4-Me-, 2-Cl-, 2-(NO_2)-, 2,4-diCl-, 2-(OMe)-, 2-(OH)-, 4-Cl-, 2,4-$(OMe)_2$-, 3-(NO_2)-, 3-(OH)-, 2,3-diCl-, 4-F-
(**1** = 1 mmol, **12** = 1 mmol, **11/11a** = 1 mmol)

form **V** which on tautomerization gave **VI**. Now,**VI** undergone cyclization form the desired product **124**.

The second reaction was completed in shorter reaction time than the first. The second reaction was carried out without any catalyst and solvent under CFL irradiation is the major merits than the first.

3.3. Metal Catalyst. Metal catalysts are also known as heterogeneous catalysts, are supported metals. However, in this subsection, some homogeneous catalysts, Lewis acid catalysts, and solid base catalysts are also there. The different types of catalysts that involved the use of conventional and nonconventional methods are discussed. Lack of toxicity, shorter reaction times, straightforward procedure, high isolated yields of the products are some of the merits of the metal catalysts.

3.3.1. Acidic inorganic catalyst. Nimmakuri and Prajapati[163] reported a Lewis acidic copper(II) triflate catalyzed synthesis of **126a** through tandem alkynylation reaction of **1** (1 mmol) with **11/11a** (1 mmol) and terminal alkynes **125** (1.2 mmol) which involved in situ generations of barbituric acid-derived Michael acceptor which upon cyclization in the presence of potassium tertiary butoxide base and the solvent, dichloroethane at 110 °C (Scheme 88). Different ERGs carrying terminal alkynes gave a good yield of **126a** compared to those carrying EWGs. Terminal alkynes with aliphatic groups ranging from 1-hexyne to 1-dodecyne gave a moderate yield, while **1** with ERGs gave a higher isolated yield of **126a** than that with EWGs.

Mobinikhaledi et al.[164] reported alum-promoted (i.e., $KAl(SO_4)_2{\cdot}12H_2O$) (10 mol %) equimolar (1 mmol) reaction of distinct **1** with **12** and **11** in water at 80 °C to attain **127** (Scheme 89). After completion, **127** was separated from reaction mixture and recrystallized using ethanol−water. The electronic nature and position of various substituents on **1** did not efficiently affect the yield of **127**. Here, alum was used as heterogeneous mild acidic, nonvolatile and noncorrosive catalyst and was insoluble in common organic solvents. This group had achieved 6-CN derivative of pyrano[2,3-*d*]-pyrimidine with higher yield in shorter reaction time and at lower temperature than the previous acidic metal catalyst based synthesis. The presence of huge numbers of pores in mesoporous silicates makes them a good host than that of acidic zeolites for bulky organic substrates which have potent connection with acidic sites on the interior surface of the mesopores. HMS (hexagonal mesoporous silica) have a wormlike pore structure. Sabour et al.[165] used heterogeneous recoverable Al-HMS-20 as catalyst (30 mg) to afford **128** through the same substrate scope in ethanol at RT (Scheme 89). The electronic nature and position of distinct electron-withdrawing or electron-releasing substituents on **1** did not affect the yield of **128**. However, heteroaromatic aldehydes also gave a high yield of **128**. Compared to the previous reaction, this group attained the 6-CN derivative in a longer reaction time at RT.

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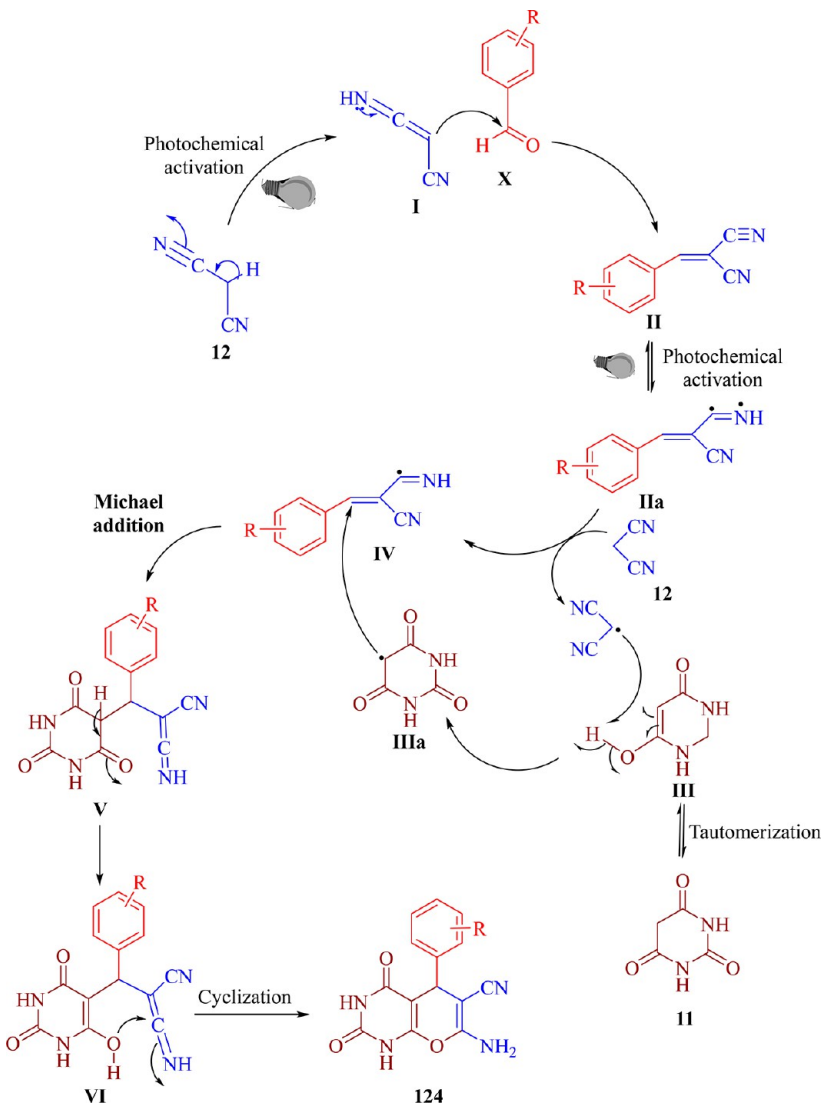
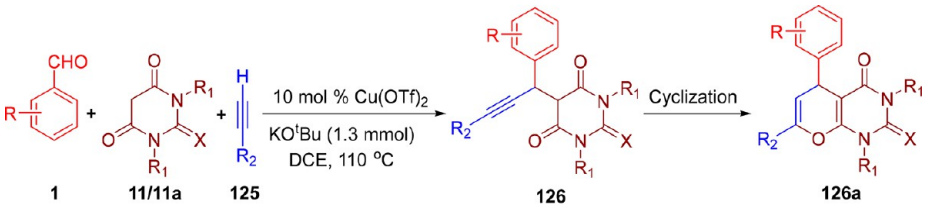


Figure 16. Synthesizing pyrano[2,3-*d*]pyrimidinediones using visible light lucency.

Scheme 88. Copper(II) Trifluoromethanesulfonate-Promoted Synthesis of 126a



Product 126a: Yield = 22-80 %, Total Entry = 23, Time = 5-32 h;
R_1 = H-/Me-; R_2 = $C_{10}H_{21}$-, C_8H_{17}-, C_7H_{15}-, C_5H_{11}-, C_4H_9-, C_2H_5-, MeO-, Me-, ^{t}Bu-, Br-, F-;
R = H-, 4-Me-, 3-Me-, 4-(OMe)-, 4-F-, 4-Cl-, 3-Cl-, 4-Br-, 4-(NO_2)-
(**1** = 1 mmol, **11/11a** = 1 mmol, **125** = 1.2 mmol)

Kumari et al.[166] afforded analogues of chromenopyranopyrimidinetriones **130** by reacting equimolar (2 mmol) diversified **1** with **11** and dimedone **129** using a Lewis acid catalyst, 5 mol % of scandium(III) triflate at 100 °C without use of any solvent (Scheme 90). The catalyst was recovered and reutilized without quantifiable loss of activity until four runs. The presence of various electron-withdrawing and electron-releasing substituents on **1** did not affect the overall yield of **130**.

Nandi et al.[167] reported In(III) chloride (35 mol %) as a Lewis-acid-promoted synthetic route which afforded naphthopyranopyrimidines-dione derivatives, namely, 8,10-dimethyl-12-aryl-12*H*-naphtho-[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-9,11-diones **131** at 120 °C without solvent via reaction of **26** (1 mmol), diversified **1** (1 mmol), and **77** (1.2 mmol) (Scheme 91). In the reaction, water and ammonia were formed as byproducts. However, the product was not obtained in absence of the catalyst even after heating up to 4 h. Distinctly

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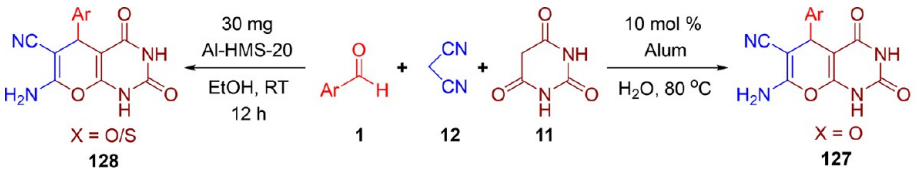
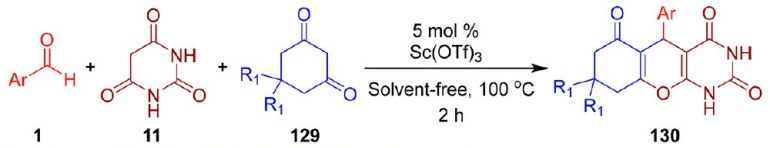
Scheme 89. Synthesizing 127 and 128 Catalyzed by Alum and Al-HMS-20, Respectively



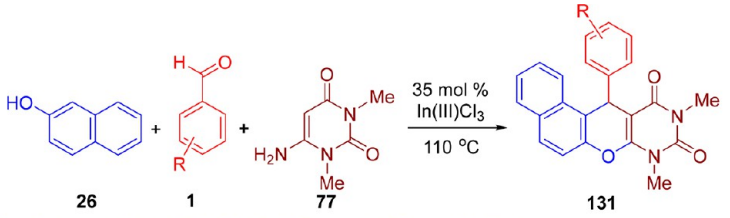
Product 127: Yield = 80-90 %, Total Entry = 8, Time = 30-45 min;
Ar = 4-Br-C_6H_4-, 3-Cl-C_6H_4-, 2,3-di-Cl-C_6H_3-, 2,4-di-Cl-C_6H_3-, 3-(OH)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NO_2)-C_6H_4-, 4-(CN)-C_6H_4-;
Product 128: X = O, Yield = 87-95 %, Total Entry = 7; X = S, Yield = 84-95 %, Total Entry = 5;
Ar = C_6H_5-, 4-Cl-C_6H_4-, 4-(NO_2)-C_6H_4-, 4-(OH)-C_6H_4-, 3-Cl-C_6H_4-, Thiophene-2-yl-, Furan-2-yl-
(In both the reactions, **1** = 1 mmol, **12** = 1 mmol, **11** = 1 mmol)

Scheme 90. Scandium Triflate-Promoted Synthesis of 130



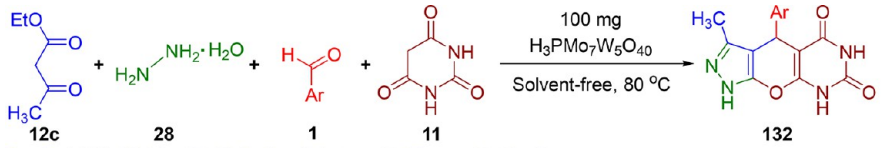
Product 130: R_1 = Me-, Yield = 95-98 %, Total Entry = 9;
R_1 = H-, Yield = 95-98 %, Total Entry = 10;
Ar = 4-(NO_2)-C_6H_4-, 4-Cl-C_6H_4-, C_6H_5-, 3-(NO_2)-C_6H_4-, 4-Me-C_6H_4-, 4-F-C_6H_4-, 4-Br-C_6H_4-, 3-Cl-C_6H_4-, 2-Nap-, 2,4-di-Cl-C_6H_3-; (**1** = 2 mmol, **11** = 2 mmol, **129** = 2 mmol)

Scheme 91. Indium Chloride-Promoted Synthesis of 131



Product 131: Yield = 67-83 %, Total Entry = 18, Time = 20-45 min;
R = H-, 4-(NO_2)-, 2-(NO_2)-, 4-(OMe)-, 2-(OMe)-, 4-Cl-, 2-Cl-, 2,4-di-Cl-, 4-Me-, 4-Br-, 4-F-, 4-(OH)-, 3-(OH)-, 2-(OH)-, 5-Br-2-(OH)-, 5-(NO_2)-2-(OH)-, 2-(OH)-3-(OMe)-, 2-(OH)-3-(OEt)-
(**26** = 1 mmol, **1** = 1 mmol, **77** = 1.2 mmol)

Scheme 92. Use of Tungsten-Based Molybdophosphoric Acid to Afford 132



Product 132: Yield = 85-96 %, Total Entry = 15, Time = 35-50 min;
R = H-, 4-Cl-, 4-(OH)-, 3-Cl-, 4-(NO_2)-, 4-(OMe)-, 3-Br-, 3-(NO_2)-, 2-(OH)-, 4-Me-, 4-F-, 3-(OMe)-, 2,4-di-Cl-, 2-Cl-, Furan-2-yl-; (Each reactant is equimolar i.e., 1 mmol)

substituted **131** gave moderate to good yield of **1**. While with aliphatic aldehydes desire product were not formed.

A large family of many transition metal oxide anions with diverse structure are known as heteropoly acids. These are made up of a connection of polyhedra, where M stands for transition metals with higher oxidation state. High Brønsted acidity, chemical stability, and their modifiable acid−base assets makes the kegging anions occupy a unique place in the leading edge of heteropoly acids (HPAs). Aher et al.[168] utilized heteropolyoxometallates, tungsten-based molybdophosphoric acid as catalyst (100 mg) to synthesize 3-methyl-4-aryl-1,4-dihydro-pyrazolo[4′,3′:5,6]pyrano[2,3-*d*] pyrimidine-5,7-(6*H*,8*H*)-diones **132** via the 4-CR of **12c** (1 mmol) with **28** (1 mmol), **1** (1 mmol) and **11** (1 mmol) at 80 °C without use of the solvent (Scheme 92). The presence of various electron-withdrawing or electron-releasing substituents on **1** did not affect the yield of **132** noticeably.

In all of these reactions, it is concluded that by changing the substrate scope different derivatives of pyrano[2,3-*d*]-pyrimidines have been obtained.

3.3.2. Basic Metal Catalyst. Lotfian et al.[169] utilized Lindqvist-type sodium salt of lanthanopolyoxometalates, i.e. $[Ln(W_5O_{18})_2]^{9-}$ (0.4 mmol), as a catalyst to afford **133** by treating equimolar (1 mmol) **11** with **12c**, **1** and **28** in water using ultrasound irradiation of 100 W (Scheme 93). At reaction termination, purified **133** was entitled followed by recrystallization using ethanol. After this, Rigi and Shaterian[170] afforded dihydropyrazolo[4′,3′:5,6]-pyrano[2,3-*d*]-pyrimidin

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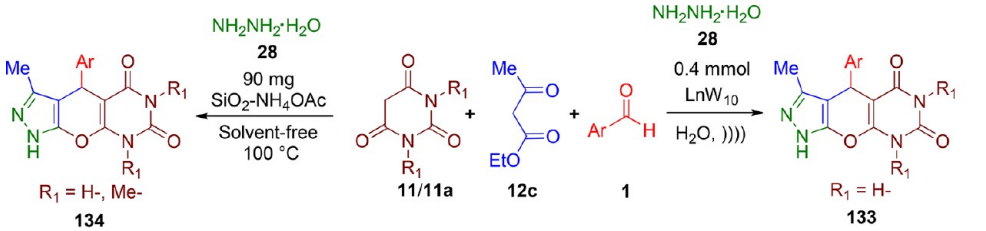
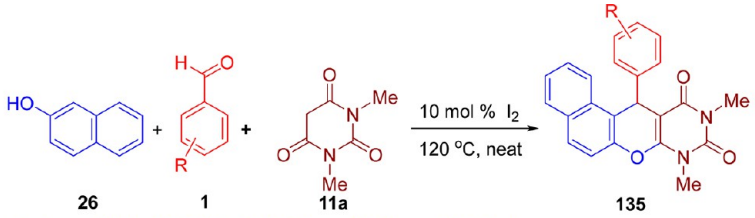
Scheme 93. Lindqvist-Type Lanthanopolyoxometalates and SiO_2−NH_4OAc as a Heterogeneous Catalyst to Afford 133 and 134



Product 133: R_1 = H-,Yield = 91-99 %, Total Entry = 20, Time = 8-18 min;
Ar = C_6H_5-, 2-(OMe)-C_6H_4-, 3-(OMe)-C_6H_4-, 3,4-di-(OMe)-C_6H_3-, 2-(OH)-C_6H_4-, 4-Me-C_6H_4-, 2-F-C_6H_4-, 3-F-C_6H_4-, 4-F-C_6H_4-, 2-Cl-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2,4-di-Cl-C_6H_3-, 2-Br-C_6H_4-, 3-Br-C_6H_4-, 4-Br-C_6H_4-, 2-(NO_2)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NO_2)-C_6H_4-, 1-Naphthyl-;
Product 134: R_1 = H-, Yield = 87-96 %, Total Entry = 14, Time = 5-6 min;
R_1 = Me-, Yield = 94-96 %, Total Entry = 6, Time = 3-5 min;
Ar = C_6H_5-, 2-(OMe)-C_6H_4-, 4-(OMe)-C_6H_4-, 3-Cl-C_6H_4-, 4-Br-C_6H_4-, 2-Cl-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NO_2)-C_6H_4-, 4-Me-C_6H_4-, 4-Cl-C_6H_4-, 3-(OMe)-C_6H_4-, 2,3-di-Cl-C_6H_3-, 2-(NO_2)-C_6H_4-, 4-F-C_6H_4-
(**11/11a** = 1 mmol, **12c** = 1 mmol, **1** = 1 mmol, **28** = 1 mmol)

Scheme 94. Neat Synthesis of 135 in the Presence of I_2



Product 135: Yield = 59-86 %, Total Entry = 12, Time = 45-80 min; (Each reactant taken in equimolar amount)
R = H-, 4-Cl-, 4-Br-, 2,4-di-Cl-, 4-F-, 3-(OPh)-, 4-Me-, 3-Cl-, 2-Br-, 2-Naphthyl-, 4-(NO_2)-, 4-(CN)-

5,7-diones **134** in the presence of heterogeneous silica-supported ammonium acetate (90 mg) as a solid base catalyst using the same substrates (equimolar, 1 mmol), **11**/**11a**, **12c**, **1**, and **28** in water at 100 °C (Scheme 93). The recovered heterogeneous catalyst was furthermore used for 4 runs. In both of the reactions, the position of different EWGs or ERGs on **1** had no noticeable effect on the yield of **133** and **134**. It could be noted that, though the yield of the product higher in case of using LnW_{10}, the reaction time could be lower in the case using SiO_2−NH_4OAc as the catalyst.

3.3.3. Miscellaneous Metal Catalyst. Kumar et al.[171] reported metal-free iodine (10 mol %) catalyzed equimolar reaction of **26** with **1** and **11a** in oil bath at 120 °C to afford **135** (Scheme 94). At reaction termination, the resultant mixture was quenched with Na_2SO_3 and taken out with ethyl acetate. This combined mixture was dried and purified using column chromatography. And finally, the pure product was recrystallized from methanol. The position of various substituents on **1** have no any notifiable effect on the product yield.

3.3.4. Metal Catalyst-Based Synthesis Involving Domino Hetero-Diels−Alder Reaction. Palasz et al.[172] described an efficient protocol which afforded *cis*−*trans* diastereomers of **TS-2**, **138** (**a**-**d**), and **139** (**a**-**d**) followed by Knoevenagel reaction of water-soluble defenseless carbohydrates (sugars) **136** and **11a** in the presence of Na_2CO_3 (sodium carbonate) in water at 80 °C; acetylation of C-glycosides **137** gave cyclic adduct **137a** which undergoes solvent-free HDA reaction with **12** (Scheme 95). In this method, all major diastereoisomers were differentiated directly from a crude reaction mixture which was then recrystallized using methanol. The ratio of major−minor of products **138** (**a**-**d**), and **139** (**a**-**d**) are (1−8.3):1.

3.3.5. Metal-Catalyzed Synthesis Involving Microwave Irradiation. Kidwai et al.[173] often carried out microwave-mediated synthesis of **141** by reacting **11** (10 mmol) with *α*,*β*-unsaturated chalcone **140** (10 mmol) using montmorillonite (15 g) (Scheme 96). When neutral alumina was used, the reaction did not complete. When acidic alumina or silica gel was used, then multiple spots on the TLC were obtained. When basic alumina (20 g) was used under the same condition, adduct **140a** was obtained which upon cyclization gave the desired **141** by using acidic montmorillonite.

Azzam and Pasha[174] determined a single-pot synthetic way to afford the trione **142** via 3-CR of substituted **1** (1 mmol) with **11** (1 mmol) and **60** (1 mmol) with an easily available base catalyst, K_2CO_3 (10 mol %), under neat MWI of 250 W (Scheme 97). The electronic nature and position of various ERGs/EWGs on **1** have no impactful effect on the yield of **142**. With aliphatic acid, the reaction did not take place. Bhosale et al.[175] also devised derivatives of **142** through a one-pot protocol to attain 5-aryl-5,6-dihydro-1*H*-pyrano[2,3-*d*]-pyrimidine-2,4,7-triones **143** using the same substrate scope in the presence of caesium carbonate (15 mol %) as a mild base catalyst under solvent-free and neat MWI conditions (Scheme 97). In both of these two reactions, the electronic nature on aryl aldehydes were not affected the isolated yield of the products **142** and **143**. However, other heteryl aldehydes also reacted well and gave 70 and 72% yield of the product in case of the second reaction, i.e., Cs_2O_3 catalyzed. Potassium carbonate-catalyzed reaction gave a higher yield in a shorter

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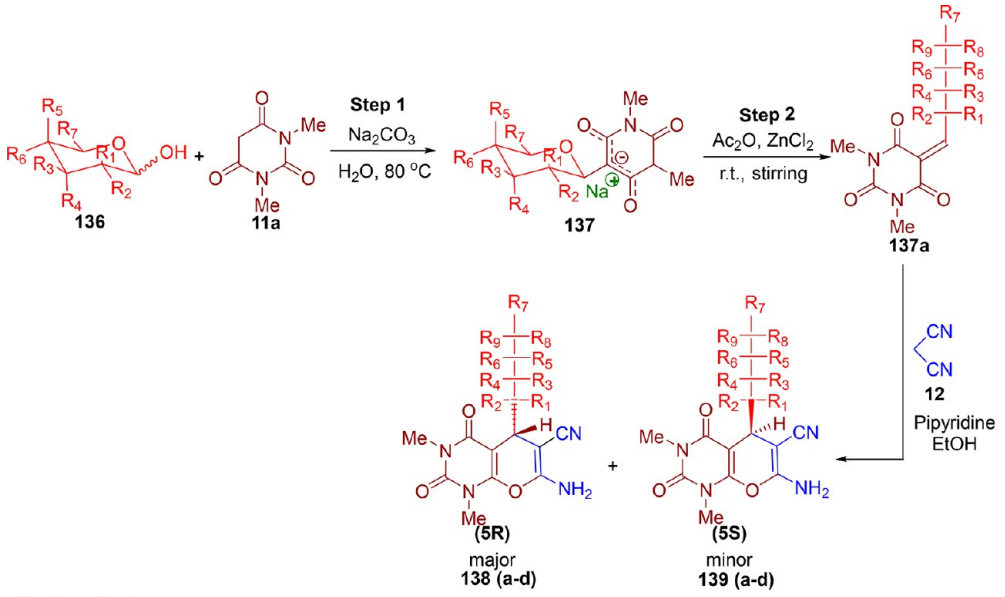
Scheme 95. Enantioselective Synthesis of 138 (a−d) and 139 (a−d)



Before step 1

L-(-)-Xylose, R_1=R_4=R_5=OH, R_2=R_3=R_6=R_7=H; L-(+)-Arabinose, R_1=R_4=R_6=R_7=H, R_2=R_3=R_5=OH; D-(+)-Glucose, R_1=R_4=R_5=H, R_2=R_3=R_6=OH, R_7=CH_2OH; D-(+)-Galactose, R_1=R_4=R_6=H, R_2=R_3=R_5=OH, R_7=CH_2OH D-(-)-Ribose

After step 2

L-xylo, R_1=R_4=R_5=R_8=AcO-, R_2=R_3=R_6=R_7=R_9=H-; L-Arabino, R_1=R_4=R_6=R_7=R_9=H-, R_2=R_3=R_5=R_8=AcO-; D-Gluco, R_1=R_4=R_5=R_8=H-, R_2=R_3=R_6=R_9=AcO-, R_7=AcO-CH_2-; D-Galacto, R_1=R_4=R_6=R_8=H-, R_2=R_3=R_5=R_9=AcO-, R_7 = AcO-CH_2-; D-Ribo, R_1=R_3=R_5=R_7=R_9=H-, R_2=R_4=R_6=R_8=AcO-, R_7= Et-, ^{t}Bu-

Product 138, 139: Total Yield = 78-84 %, Total Entry = 4, Time = 3-6 h;

a. L-Xylo, R_1=R_4=R_5=R_8=AcO-, R_2=R_3=R_6=R_7=R_9=H-;

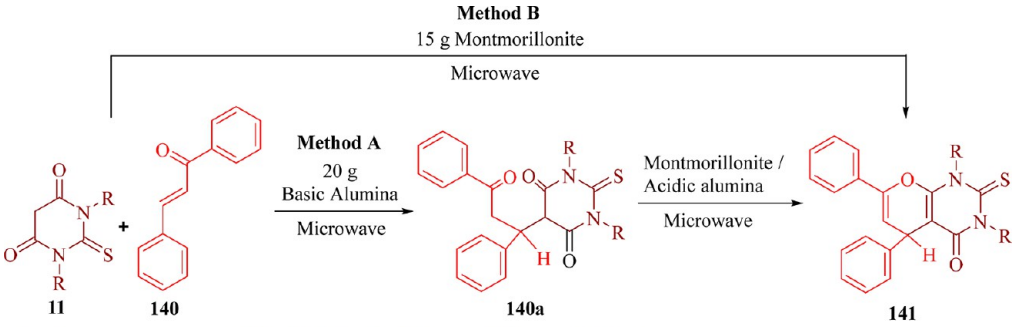
b. L-Arabino, R_1=R_4=R_6=R_7=R_9=H-, R_2=R_3=R_5=R_8=AcO-;

c. D-Gluco, R_1=R_4=R_6=R_8=H-, R_2=R_3=R_6=R_9=AcO-, R_7=AcO-CH_2-;

d. D-Galacto, R_1=R_4=R_6=R_8=H-, R_2=R_3=R_5=R_9=AcO-, R_7=AcO-CH_2-;

Ratio of major/minor = (1-8.3):1; ($ZnCl_2$ = 73.5 mmol, Ac_2O = 50 mL, **137** = 4 mmol)

Scheme 96. Microwave-Irradiated Synthesis of 141 Using Method A and Method B



Product 141: Method A, Yield = 83-88 %, Total Entry = 6, Time = 1.5-2.3 min;

Method B, Yield = 90-93 %, Total Entry = 6, Time = 3.2-3.5 min;

R = H-, Ph-, 2-(OMe)-Ph-, 4-(OMe)-Ph-, 2-Me-Ph-, 4-Cl-Ph-; (**11** = 10 mmol, **140** = 10 mmol)

reaction than the cesium carbonate-catalyzed reaction under neat microwave irradiation.

3.3.6. Metal-Catalyzed Synthesis Using the Electrolysis Method. With wider application of the environmentally friendly procedure, higher yields are some of the major advantages of using electrolysis as a nonconventional method. Elinson et al.[176] also used an electrolytic technique to afford **144** along with their diversified analogues using a three-component equimolar (5 mmol) reaction of **1**, **11a**/**11b**, and **12** in ethanol as a solvent and an electrolyte, sodium bromide (0.5 mmol), at 78 °C (Scheme 98). During the reaction, a constant current density, 0.005 A cm^{-2} and 0.1 F mol^{-1} delivered in an undivided cell. The reaction was completed in nearly 30 min. Afterward, Kefayati et al.[177] used an electrochemical method to acquire **145** through equimolar (2 mmol) reaction of **1**, **11**, and **12** in ethanol at RT with 0.21 mmol electrolyte, KBr (Scheme 98). An undivided cell carrying cathode (iron electrode) and anode (graphite electrode) with potassium bromide as an electrolyte was used in this method. This method involved the use of a three-electrode platinum as the working electrode, Ag-AgCl as the reference electrode, and glassy carbon as the counter electrode.

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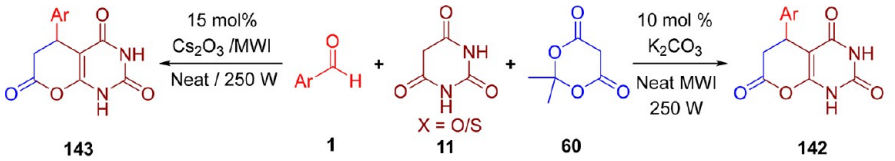
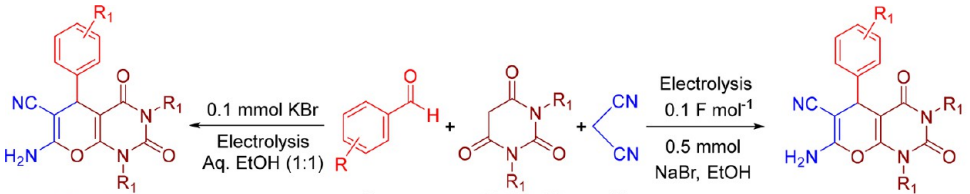
Scheme 97. Neat MWI-Mediated Synthesis of 142 and 143 Using K_2CO_3 and Cs_2O_3



Product 142: Yield = 95-97 %, Total Entry = 9, Time = 40-60 seconds;
Ar = 4-(NO_2)-C_6H_4-, 2-(OH)-C_6H_4-, 2-(NO_2)-C_6H_4-, 2-Cl-C_6H_4-, 2,4-di-(OMe)-C_6H_3-, 4-F-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-Cl-C_6H_4-, 3,4-di-(OMe)-C_6H_3-;

Product 143: Yield = 70-92 %, Total Entry = 14, Time = 120-130 min;
Ar = 4-(NO_2)-C_6H_4-, 2-(OH)-C_6H_4-, 4-Br-C_6H_4-, 4-(OH)-C_6H_4-, 4-Me-C_6H_4-, 4-Cl-C_6H_4-, 2-Cl-C_6H_4-, 4-(OMe)-C_6H_4-, 5-Br-thiophyl-, 4-F-C_6H_4-, 3,4-di-(OMe)-C_6H_3-, 4-(NMe_2)-C_6H_4-, Furan-2-yl-, 4-(OH)-3-(OMe)-C_6H_3-; (In both the reactions, **1** = 1 mmol, **11** = 1 mmol, **60** = 1 mmol)

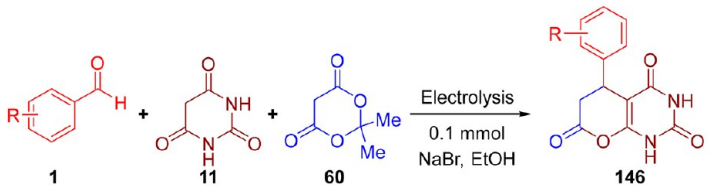
Scheme 98. Electrolytic Method to Afford 144 and 145 Using NaBr and KBr as an Electrolyte



Product 144: R_2 = Me-, Yield = 71-81 %, Total Entry = 8; R_2 = Et-, Yield = 73-76 %, Total Entry = 2;
R = 2-Cl-, 4-F-, H-, 4-Me-, 4-(OMe)-, 4-Cl-, 3-Br-, 4-(NO_2)-; (**1** = 5 mmol, **11/11a/11b** = 5 mmol, **12** = 5 mmol)

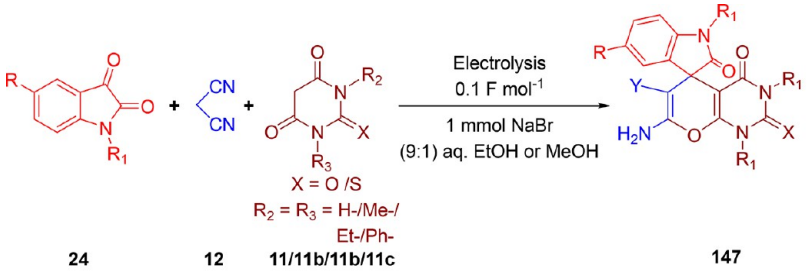
Product 145: Yield = 92-97 %, Total Entry = 8, Time = 4 h; (**1** = 2 mmol, **11/11a/11b** = 2 mmol, **12** = 2 mmol)
R = 2-(OH)-, 2-Cl-, 4-Cl-, 2-(NO_2)-, 2,4-di-(OMe)-, 3,4-di-(OMe)-, 3-(NO_2)-

Scheme 99. Synthesizing 146 in Ethanol Using the Electrolysis Method



Product 146: Yield = 92- 97 %, Total Entry = 8, Time = 4 h;
R = 2-(OH)-, 2-Cl-, 4-Cl-, 2-(NO_2)-, 4-(NO_2)-, 2,4-di-(OMe)-, 3,4-di-(OMe)-, 3-(NO_2)-
(**1** = 1 mmol, **11** = 1 mmol, **60** = 1 mmol)

Scheme 100. Electrolysis-Promoted Synthesis of 147 Using NaBr



Product 147: Yield = 78-95 %, Total Entry = 11, Time = 64 min;
R = H-, Br-; R_1 = H-, Me-, Ac-; (**24** = 10 mmol, **12** = 10 mmol, **11/11b/11c** = 10 mmol)

The reaction was completed in 22 min. Reaction progress was measured using three ways: (1) cyclic voltammetry, (2) thin layer chromatography, and (3) electrical charge-time plot. Both reactions were not affected by the nature and position of various substituents on **1** have not affected the yield of **145**. Compared to NaBr, the KBr electrolysis method gave a higher yield of the product.

Veisi et al.[178] demonstrated a novel and electrochemical method to prepare various analogues of pyranopyrimidine-trione **146** using an undivided cell via single-pot 3-CR of **1** (1 mmol) with **11** (1 mmol) and **60** (1 mmol) in the presence of electrolyte sodium bromide (0.1 mmol) in ethanol at RT (Scheme 99). In this method, acetone and carbon dioxide got eliminated. This method involved in situ generation of base. An undivided cell was made up of iron electrode (cathode)

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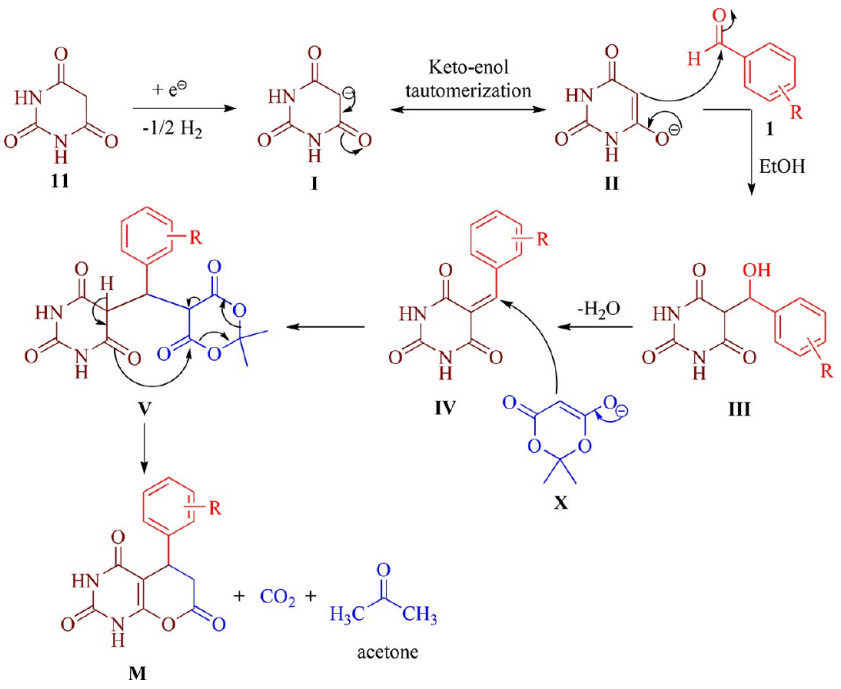


Figure 17. Proposed mechanism to afford **M** using the electrolysis method.

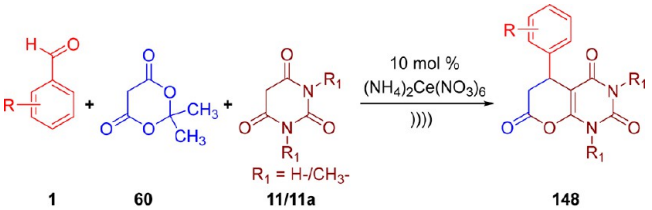
and graphite (anode) with the perpetual current density, 0.01 A cm^{-2}, and translactonization. **1** consisting of either ERGs/EWGs had no quantifiable effect on the yield of **146**.

Elinson et al.[179] demonstrated the synthesis of 7′-amino-2,2′,4′-trioxo-1,1′,2,2′,3′,4′-hexahydrospiro[indole-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitriles **147** using the equimolar (10 mmol) reaction of **24** with **12** and **11**'s derivatives using the undivided cell with graphite (anode) and iron (cathode) at 20 °C in ethanol (Scheme 100). The reaction was proceeded by passing a constant current condensity, 5 $mAcm^{-2}$ with 0.1 F mol^{-1} amount of electricity. As the electrolysis was completed, the desired product was directly recrystallized from the reaction mixture. The involvement of electrochemically activated chain process permitted the formation of high product yield. The slight decrease in yield of **147** was observed as the density of current was increased.

The probable mechanistic pathways to afford pyrano[2,3-*d*]pyrimidinedione/trione using electrolysis method was shown Figure 17. However, in Elinson's method, an active methylene group containing malononitrile was used. Abstraction of a proton from the active methylene group of barbituric acid **11** generates a barbiturate anion **I** that undergoes keto−enol tautomerism to give the anion **II**. Now, the carbonyl carbon of an aromatic aldehyde **1** was attacked by the anion **II** to afford **III** which on the removal of the water molecule gave **IV**. As shown in the mechanism enolic form of dimedone **X** attacks on **IV** to generate **V** which upon cyclization gave the desired product pyrano[2,3-*d*]pyrimidinedione/trione **M** along with the removal of carbon dioxide and acetone.

3.3.7. Metal-Catalyst-Based Synthesis Utilizing Ultrasound Irradiation. Ultrasound irradiation is known as sonochemistry and is a sound of a frequency to which the human ear can respond. Cavitation is the driving force of sonochemical reactions, thus required at least one phase of the reaction mixture must be a liquid. Cavitation is generated above 20 and 40 kHz. However, beyond 5 MHz frequency does not produce any cavitation.[180] In this regard, Dandia et al.[181] utilized cerium(IV) ammonium nitrate (10 mol %) as catalyst and gave single-pot route to synthesize **148** through equimolar (2 mmol) treatment of **1** with **60** and **11**/**11a** in water under ultrasound irradiation (Scheme 101). The catalyst used here have Lewis acid properties as well as electron-transfer capacity. After reaction completion, **148** was recrystallized form ethanol. The electronic nature and position of various electron-donating and electron-withdrawing substituents on **1** have no any notifiable effect on the yield of **148**. When **11a** was used instead of **11**, the reaction proceeded with a lower rate due to the lower acidity of the methylene proton than barbituric acid. No need of base, good functional group tolerance are some of the major merits of using ceric ammonium nitrate as the catalyst in ultrasound irradiation as a nonconventional methods.

Scheme 101. Ceric Ammonium Nitrate-Promoted Synthesis of 148 Using Sonication



Product 148: R_1 = H-, Yield = 94-96 %, Total Entry = 6, Time = 26-32 min; R_1 = CH_3-, Yield = 83-86 %, Total Entry = 2, Time = 37-40 min; R = 4-Cl-, 4-(NO_2)-, 4-F-, 2-(NO_2)-, 2-Cl-, 2-(OH)- (**1** = 2 mmol, **60** = 2 mmol, **11**/**11a** = 2 mmol)

The possible mechanism for synthesis of **148** under sonication condition is shown in Figure 18. Initially, cerium-(+IV) ion coordinate with the carbonyl oxygen of an aromatic aldehyde on which Knoevenagel condensation reaction took place with **11**/**11a** to give the adduct **I**. Now, the Michael addition of adduct **I** with **II** facilitated by coordination with Cerium(+IV) ion to give intermediate **III**, which cyclize to give

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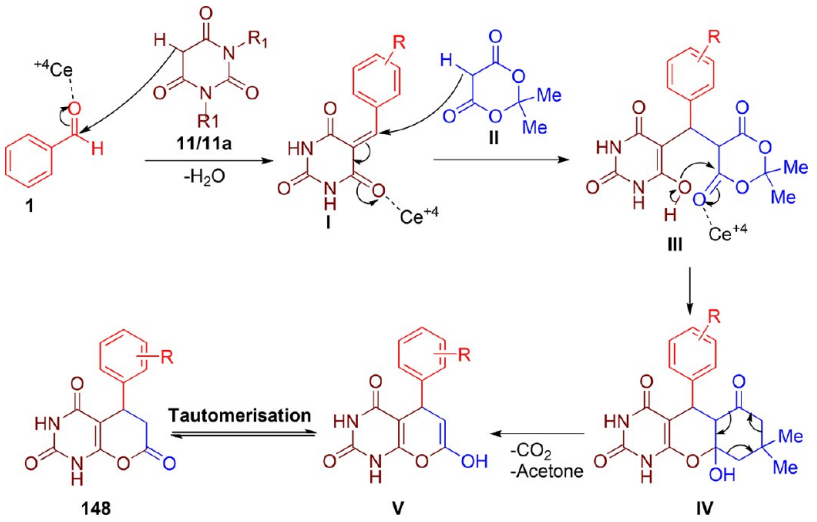
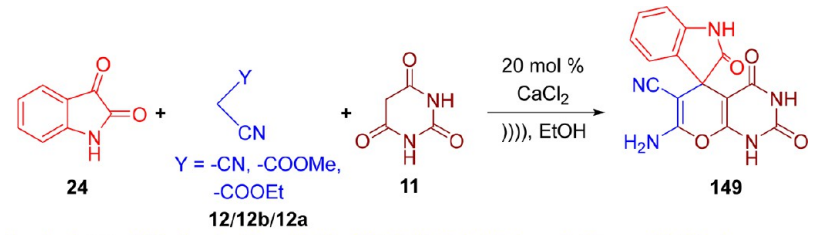


Figure 18. Proposed mechanism for $(NH_4)_2Ce(NO_3)_6$ promoted synthesis of **148** using sonication.

Scheme 102. Use of Sonication to Afford 149



Product 149: With Sonication, Yield = 91-95 %, Total Entry = 4, Time = 12-18 min;
Without Sonication, Yield = 90-93 %, Total Entry = 4, Time = 160-190 min
(**24** = 1 mmol, **12/12b/12a** = 1 mmol, **11** = 1 mmol)

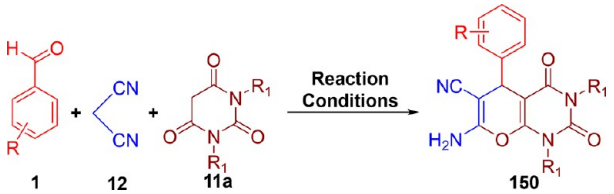
the tricyclic intermediate **IV**. This **IV** on removal of acetone and carbon dioxide gave **V**. Further, **V** on tautomerization gives the desired product **148**.

Safaei et al.[182] treated **24** (1 mmol) with **11** (1 mmol) and **12/12b/12a** (1 mmol) to get **149** in the presence of 20 mol % of $CaCl_2$ in ethanol at RT (Scheme 102). The reaction was carried out with/without sonication. After completion, **149** was recrystallized from ethanol. The overall yield of **149** did not got affected by nature and position of various substituents. However, the use of environmentally friendly solvent and RT with higher reaction yield are the major benefits of using this method.

3.4. Green-Solvent-Promoted Synthesis. A solvent can act either as medium or participate in reaction itself in the synthetic organic chemistry. Their microscopic properties like hydrogen bonding ability, dipole moment, and its macroscopic properties such as density should be considered when carrying out a chemical reaction. Moreover, solvent can stabilize intermediates, bring the reaction to equilibrium, increase reaction rate, can act as an acid or base, hence increase or decrease speed of reaction and even change the course of the reaction. A solvents are often volatile, hazardous, flammable, affect human health and the environment by ozone-layer depletion.[183] Greener solvents are relatively nontoxic and nonhazardous[184] such as water, biodegradable solvents like poly(ethylene glycol), ethanol, organic carbonates are thus gained more importance in chemical reaction. This section involved the collection of various synthetic pathways to afford analogues of **TS-2** only in the presence of the solvent media. The protocol was performed successfully. PEG-400, ethanol, water, ethanol−water, magnetic deionized water, etc. are some of the solvents which covered in this subsection.

Shaabani et al.[185] developed **150** via condensation reaction of **1** with **12** and **11a** in water at 80 °C without catalyst (Scheme 103 and Table 7, entry 1). Here, hydrophobic nature

Scheme 103. Various Reaction Conditions for the Synthesis of Analogues of Compound 150



and internal pressure promoted activation of three substrates in solvent's cavity. The reaction was completed in 11 h and gave 81% yield of **150**. Finally, **150** was purified through washing with water.

Table 7 shows various reaction conditions for the production of derivatives of **150** followed by one-shot three-component equimolar reaction of aromatic aldehyde **1**, malononitrile **12**, and 1,3-dimethyl barbituric acid **11a**. Herein, different green solvents reported earlier are covered such as water, PEG-400, magnetic deionized water, and ethanol. From Table 7 we say that changing the solvent and temperature affects the yield of the product and also the reaction time.

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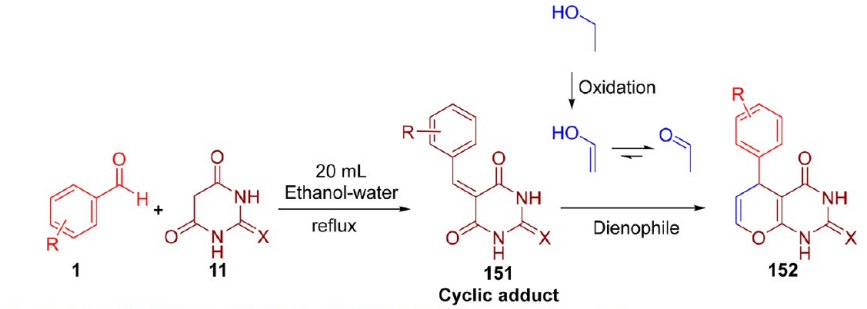
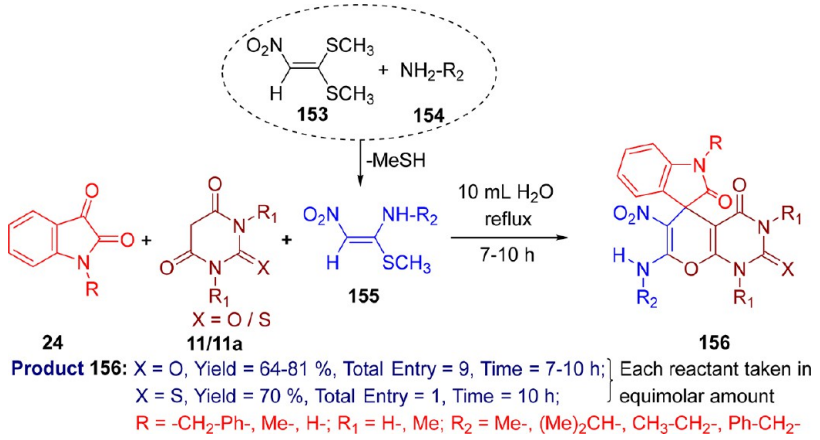
Table 7. Various One-Pot 3-CR Routes to Synthesize 150 by Utilizing Different Green Solvents

entry	reaction condition (catalyst/solvent, temperature)	yield (%)	reaction time	ref
1	20 mL of water, 80 °C	81	11 h	Shaabani et al.[185]
2	3 mL of PEG-400, 100 °C	76−95	70−120 min	Mohamadpour[186]
3	5 mL of MDW, 70 °C	82−97	45−100 min	Bakherad et al.[187]
4	Method A: 10 mL of EtOH, 60 °C, reflux	20−59	180−300 min	Jonnalagadda et al.[188]
	Method B: 10 mL of aq EtOH, 30 °C, ultrasound irradiation (50 kHz, 150 W)	90−99	1−5 min	

Scheme 104. Use of [4+2] Cycloaddition to Afford 152



Scheme 105. Synthesizing 156 Using Refluxing Condition



Mohamadpour[189] synthesized the analogue of **150** using poly(ethylene glycol)-400 catalyst at 100 °C. This protocol gave higher yield in shorter reaction time than entry 1 (Table 7). Bakherad et al.[187] devised derivatives of **150** using magnetic deionized water at lower temperature gave comparatively higher yield in lower reaction time than entries 1 and 2 (Table 7). Jonnalagadda et al.[188] developed novel analogue of **150** using two different methods, in which Method 1 involved the use of ethanol at 60 °C, giving only 20−59% yield and taking a higher reaction time than entries 2 and 3 (Table 7). Method 2 involved the use of aqueous ethanol at 30 °C under ultrasound irradiation, giving the highest isolated yield of **150** in just 1−5 min than all the other entries in Table 7.

Zidar and Kikelj[190] synthesized **152**, i.e., 5-aryl-1*H*-pyrano-[2,3-*d*]-pyrimidine-2,4(3*H*,5*H*)-diones(2-thiones). They used the domino Knoevenagel-HAD/oxidation-HDA reaction in which the heterodiene and dienophile were in situ generated through treatment of **11** and **1** and oxidation of ethanol. Treatment of **1** (1 mmol) with **11** (1 mmol) occurred in 20 mL of aqueous ethanol under reflux for 3 days (Scheme 104). Similarly, the starting materials were heated at 120 °C in a closed sealed glass vessel using microwave reactor. Thereafter, the resultant mixture was cooled to RT and the isolated yield of **152** was washed with ethanol. The reaction with electron-withdrawing substituents on **1** proceeded smoothly. However, when solvents other than ethanol were used such as propanol, isopropanol have no effect on the final yield of **152**. Thus, the steric factor played key role for dienophiles.

Ghadiri and co-workers[191] developed a greener synthetic route to afford a novel analogue of spiropyranopyrimidine, **156**, by using a three-component equimolar reaction of **24** with **11**/**11a**, and *N*-alkyl-1-(methylthio)-2-nitroethenamine **155** was derived via the reaction of discrete amine **154** with nitroketene dithioacetal **153** in green solvent water (10 mL) under reflux for 7−10 h (Scheme 105). Reactions showed in Scheme 105 took highest reaction time than the other reaction in this section of the present review.

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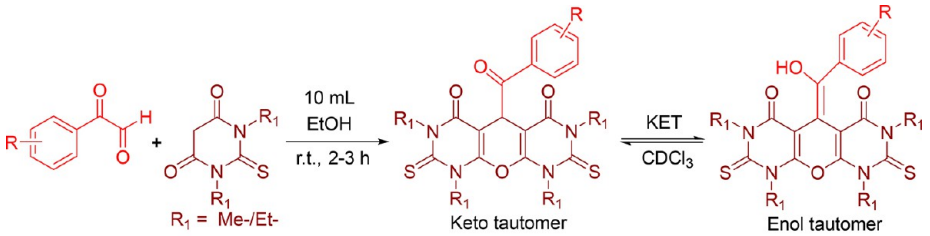
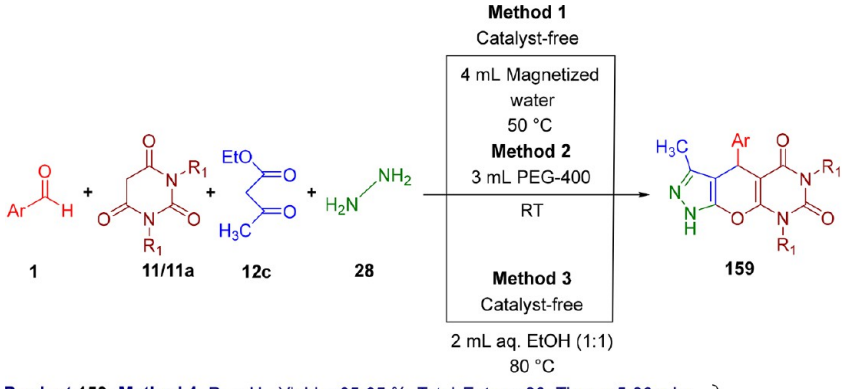
Scheme 106. Chemoselective Synthesis of 158a in Alcohol



Product 158a: R_1 = Et-, Yield = (Keto: Enol) = ((33-56):(44-67)) %, Total Entry = 10;
R_1 = Me-, Yield = (Keto: Enol) = ((35-100):(0-65)) %, Total Entry = 9;
R = H-, 4-Br-, 4-Cl-, 4-F-, 4-(NO_2)-, 4-(OMe)-, 3-Br-, 3-(OMe)-, 3,4-di-(OMe)-, 3,4-(OCH_2O)-
(**157** = 1 mmol, **11a/11b** = 1 mmol)

Scheme 107. Using Magnetic Deionized Water in the Synthesis of 159



Product 159: Method 1, R_1 = H-, Yield = 85-95 %, Total Entry = 20, Time = 5-20 min;
Method 2, R_1 = H-, Yield = 89->99 %, Total Entry = 15, Time = 25-60 min;
R_1 = Me-, Yield = 84-94 %, Total Entry = 4, Time = 70-85 min;
Method 3, R_1 = H-, Yield = 90-97 %, Total Entry = 12, Time = 20-35 min;
} Each reactant taken in equivalent amount
Ar = C_6H_5-, 4-Cl-C_6H_4-, 4-(NO_2)-C_6H_4-, 4-Me-C_6H_4-, 4-(OMe)-C_6H_4-, 4-(OH)-C_6H_4-, 2,4-di-Cl-C_6H_3-, 3,4-di-(OMe)-C_6H_3, 4-(OH)-3-(OMe)-C_6H_3-, 4-(NMe_2)-C_6H_4-, 3-(OH)-C_6H_4, 2-(OMe)-C_6H_4-, 2-Cl-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-Br-C_6H_4-, 3-Br-C_6H_4-, 3-F-C_6H_4-, 2,6-di-Cl-C_6H_3-, 2-(NO_2)-C_6H_4-, 2'-furanyl, 2'-pyridinyl-, 4-(CHO)-C_6H_4,2,3,4-tri-(OMe)-C_6H_2-, 3,5-di-(OMe)-C_6H_3-, 2,Cl-quinolone-3-yl-

Rimaz et al.[192] developed the chemo- and regioselective synthesis of a novel symmetric fused **158a** through the reaction of arylglyoxal **157** (1 mmol) with **11a/11b** (1 mmol) in absolute alcohol (10 mL) at room temperature for appropriate hours (Scheme 106). The enol form **158a** was stable only in solution phase and all the compounds were gained in keto form **158**. Arylglyoxal **157** with either ERG/EWG did not affect the isolated yield of **158** efficiently. This group has synthesized novel derivatives of pyrano[2,3-*d*]pyrimidin-2-thiodione.

The novel pyrazolopyranopyrimidine **159** and its diverse analogues were synthesized under catalyst-free conditions. For this purpose, Bakherad and co-workers,[193] Kardooni and Kiasat,[186] and Rathinam et al.[194] carried out a three-component equimolar reaction of **1**, **11/11a**, **12c**, and **28** under catalyst-free conditions in 4 mL of magnetized water at 50 °C, PEG-400 (3 mL) at RT, and 2 mL of aqueous EtOH at 80 °C (Scheme 107). In Method 1, the magnetized water used here was prepared using a static magnetic system with a field strength of 6000 G with 500 mL s^{-1} for up to 10 min. It was observed that freshly prepared magnetized water gave a higher yield of **159**. But the magnetized water gave less product as the time from magnetization of the water increased. In all three reactions, the pure product **159** was attained using ethanol. Also, an isolated yield of the product **159** remain unaffected by the presence of various ERG/EWG on an aromatic ring of aryl aldehyde. Synthesizing **159** using Method 3 gave higher yield as well as in shorter reaction time compared to Methods 1 and 2. In addition, Kardooni and Kiasat[186] synthesized barbituric acid as well as 1,3-dimethyl-barbituric acid derivatives, while two other groups synthesized only barbituric acid derivative of **159**.

3.5. Catalyst-/Solvent-Free Neat Synthesis. Much less work has been found to synthesize **TS-2** under solvent-/catalyst-free conditions. This is because of limitations of catalyst-free and solvent-free route such as selecting active starting materials, long reaction time and side products, use of excess reagents or reactant, selectivity of products, less applicability in-solid-state synthesis, use of high temperature and pressure, and solubility of reactants and reagents. In this regargd, Mashkouri and Jamal[195] reported the catalyst-free and solvent-free synthesis of **160** through the reaction of **1** (1 mmol) with **12** (1 mmol) and **11** (1 mmol) by ball milling in a stoichiometric amount (Scheme 108). Ball milling is a mechanical technique that is widely used to attain fine particles simply by grinding the minerals and in modification of inorganic solids. The isolated yield of **160** was not affected by the position and electronic nature of desrete substituents on **1**. The main benefits of this methods includes catalyst- and

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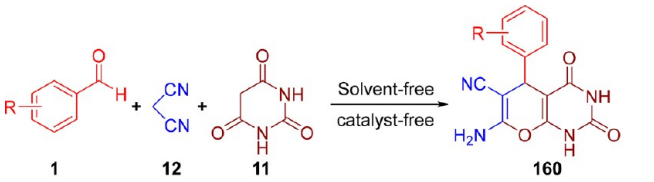
Scheme 108. Utilizing Ball Milling Technique to Afford 160 in the Absence of Catalyst and Solvent



Product 160: Yield = >99 %, Total Entry = 8, Time = 15-90 min;
R = H-, 2-Cl-, 4-Cl-, 2-(NO_2)-, 3-(NO_2)-, 4-(NO_2)-, 4-Br-, 4-(OMe)-
(**1** = 1 mmol, **12** = 1 mmol, **11** = 1 mmol)

solvent-free condition and providing higher yield of **160** in shorter time copmared to others.

3.6. Ionic-Liquid-Catalyzed Synthesis. Nowadays, in organic synthesis, ILs have generated a great deal of attention due to their high selectivity that adds green values in ongoing research. This section consists of the synthesis of diverse analogues of the **TS-2** scaffold using different types of ILs. A common mechanism for IL-promoted synthesis of derivatives of **TS-2** is shown in Figure 19. Initially, by hydrogen bonding with Brønsted acidic ILs, the carbonyl group of an aromatic aldehyde was activated with lower energy of the transition state. Now, the reaction takes place in two different pathways. In the first pathway, Knoevenagel condensation reaction between activated aldehyde **II** and barbituric acid derivatives **III** formed **IV**, which gave **V** by water removal. Now, **V** was nucleophilically attacked by **IIIa** to afford **VI**. In the second pathway, the Knoevenagel condensation reaction took place between activated aldehyde **II** and malononitrile **IIa** to give **IVa**, which upon removal of water molecule gave **Va**. Now, the nucleophilic attack of barbituric acid derivatives **III** on **Va** constructed **VI**. Now, this **VI** on intramolecular cyclization yielded the desired product **M**.

With ILs being an environmentally friendly solvent as well as a catalyst, Yadav and Quaraishi[196] synthesized **161** by 3-CR of **1** (2 mmol) with **12** (2 mmol) possessing an active methylene group and **11** (2 mmol) catalyzed by Lewis acidic choline chloride $ZnCl_2$ IL (0.5 mmol) and triethanolamine as a base in a small amount of ethanol solvent at 75 °C to afford **161** (Scheme 109). This was the conventional method. Although when ultrasonic irradiation was used at the same temperature, the rate of reaction got increased and completed in a very short time. **1** with electron-withdrawing substituents produced a

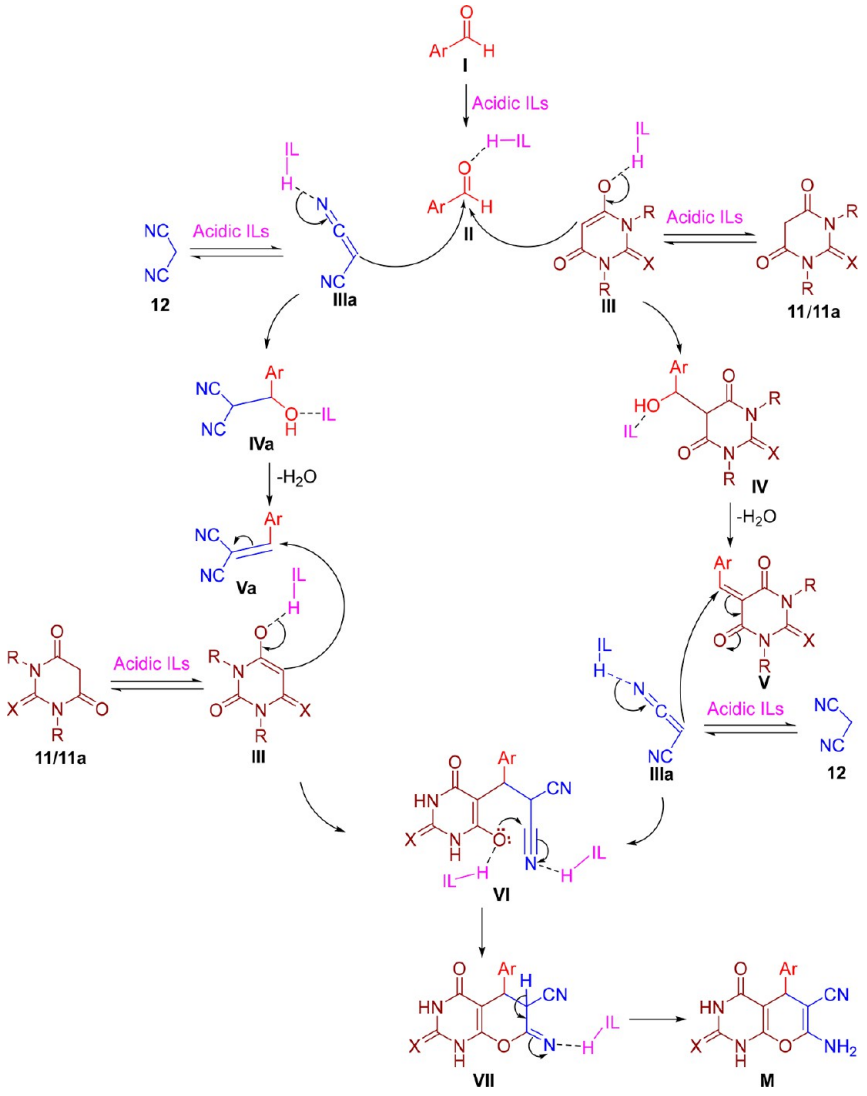


Figure 19. Proposed reaction mechanism for IL-catalyzed pyranopyrimidinediones (triones).

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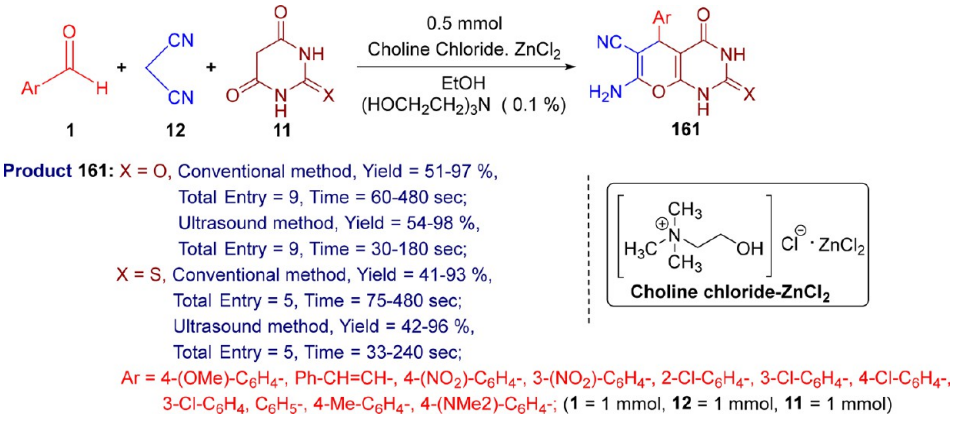
Scheme 109. ChCl-$ZnCl_2$-Promoted Synthesis of 161



Scheme 110. Synthesis of Various Analogues of 162 Using Different Reaction Conditions

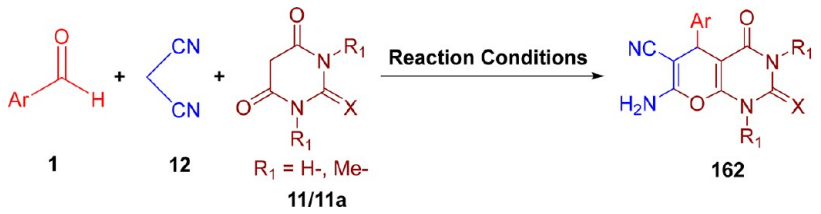


Table 8. Various Reaction Conditions to Produce Analogues of Scaffold 162

entry	reaction condition (ILs, solvent, temperature)	yield (%)	reaction time	ref
1	Method 1: $[DABCO](HSO_3)_2(Cl)_2$ (17 mg), H_2O, reflux	80−93	7−40 min	Shirini et al.[197]
	Method 2: $[DABCO](SO_3H)_2(HSO_4)_2$ (17 mg), H_2O, reflux	80−95	5−35 min	
2	$[SuSA\text{-}H]HSO_4$ (0.05 mmol), H_2O, 80 °C	85−98	7−30 min	Abedini et al.[198]
3	$[H\text{-}Suc]HSO_4$ (10 mg), H_2O, oil bath, 80 °C	85−98	5−15 min	Shirini et al.[199]
4	$[H_2\text{-}DABCO]_9[H_2PO_4]_2$ (20 mg), H_2O, 75 °C	80−95	8−30 min	Shirini et al.[200]
5	$[H_2\text{-}Bisim][HSO_4]_2$ (6.2 mol %), H_2O, reflux	50−96	5−120 min	Shirini et al.[201]
	$[H_2\text{-}Bisim][ClO_4]_2$ (7.6 mol %), H_2O, reflux	58−96	10−120 min	
6	[TPPHSP]Br (2 mol %), aq EtOH, reflux	76−95	35−90 min	Momeni et al.[202]
7	$[C_4(Mim)_2]\cdot 2Cl$ (30 mg), H_2O, reflux	80−90	15−25 min	Shirini et al.[203]
	$[C_4(Mim)_2]\cdot 2HSO_4$ (20 mg), H_2O, reflux	87−94	20−30 min	
8	$[(DABCO)_2C_3H_5OH]\cdot 2Cl$ (8.5 mol %), H_2O, reflux	80−93	1 h	Shirini et al.[204]
		80		
9	Method A (conventional method): [L-proline]NO_3 (15 mol %), H_2O, 80 °C	82−92	12−15 min	More et al.[205]
	Method B (sonication assisted): [L-proline]NO_3 (15 mol %), open flask, H_2O	86−95	4−12 min	
10	$[C_4(DABCO)_2]\cdot 2(OH)$, H_2O (2 mol %), oil bath, 80 °C	85−96	4−10	Shirini et al.[206]
11	agar-entrapted $[DABCO](SO_3H)_2(Cl)_2$ (50 mg), H_2O, reflux	94.4−99.1	8−15 min	Shirini et al.[207]
12	bead-PIL (20 mg), water, 25 °C	90−100	20 min	Koohestani and Sadjadi[208]
13	3 mol % of IL-MIL-101(Fe), aq EtOH	80−100	2 h	Sadjadi and Koohestani[209]
14	$[H_2\text{-}BiPy][ClO_4]_2$ (10 mg), H_2O, reflux	87−96	7−30 min	Shirini et al.[210]

higher yield of **161** than those carrying electron-donating substituents.

Thereafter, different groups came and synthesized novel derivatives of **162** through single-shot 3-CR reaction of **1** with **12** and **11**/**11a** using different ILs with solvent at a particular temperature as shown in Scheme 110 (Table 8, entries 1−14). Only in entry 9, R_1 = Me-; otherwise in all entries, R_1 = H-. Also, In entries 1, 4, 8, and 11, X = O/S, while in all other entries, X = O.

Table 8 shows diverse reaction conditions by utilizing ILs to synthesize pyrano[2,3-*d*]pyrimidinone/thione **162** through the one-pot three-component reaction of aryl aldehyde **1**, malononitrile **12**, and barbituric acid derivatives **11**/**11a**. Each reaction was carried out in equimolar (1 mmol) amount except in entries 2, 7, and 14 where the amount of **1** and **11**/**11a** (1 mmol) and amount of malononitrile **12** was 1.2 mmol, 1.1 mmol, and 1.1 mmol, respectively. Here various ionic liquids such as $[SuSA\text{-}H]HSO_4$, $[H\text{-}Suc]HSO_4$, $[H_2\text{-}DABCO]_9[H_2PO_4]_2$, $[H_2\text{-}Bisim][HSO_4]_2$ or $[H_2\text{-}Bisim][ClO_4]_2$, $[C_4(Mim)_2]\cdot 2Cl$ or $[C_4(Mim)_2]\cdot 2HSO_4$, $[(DABCO)_2C_3H_5OH]\cdot 2Cl$, $[C_4(DABCO)_2]\cdot 2(OH)$, agar-entrapped $[DABCO](SO_3H)_2(Cl)_2$, $[H_2\text{-}BiPy][ClO_4]_2$, [TPPHSP]Br, [L-proline]NO_3, bead-PIL, and IL-MIL-101(Fe) were reported for the synthesis of **162**. Shirini et al.[207] did a case study of the synthesis of pyrano[2,3-*d*]pyrimidine derivatives. From the table, entries 11 and 12 showed that by using these reaction conditions, higher isolated yield of the product were obtained in shorter reaction time. In entry 13, 80−100% yield of the

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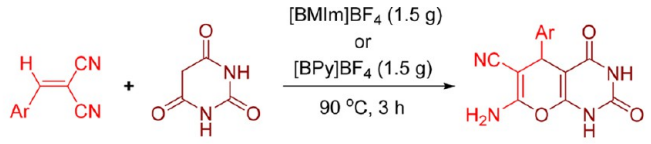
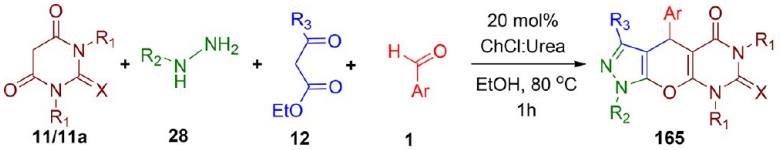
Scheme 111. [BMIm]BF_4/[BPy]BF_4-Promoted Synthesis of 164



163 11 164

Product 164: Yield = 84-95 %, Total Entry = 6, Time = 3-5 min;
Ar = H-, 4-Cl-, 2-Cl-, 4-F-, 2,4-di-Cl-, 3,4-di-(OMe)-; (**163** = 5 mmol, **11** = 5 mmol)

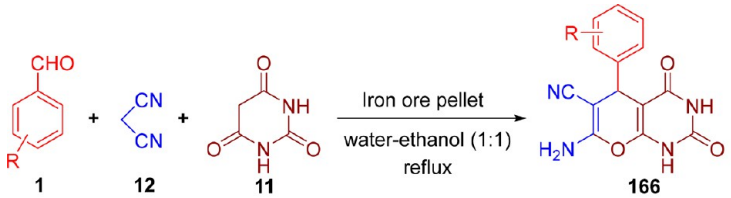
Scheme 112. Deep Eutectic Mixture of ChCl/Urea as a Catalyst to Afford 165



11/11a 28 12 1 165

Product 165: X = O, R_1 = H-, R_2 = H-, R_3 = Me-, Yield = 75-92 %, Total Entry = 20;
R_1 = H-, R_2 = H-, R_3 = Ph-, Yield = 75 %, Total Entry = 1;
R_1 = H-, R_2 = Ph-, R_3 = Me-, Yield = 75-84 %Total Entry = 2;
R_1 = Me-, R_2 = R_3 = Me-, Yield = 82 %,Total Entry = 1;
X = S, R_1=R_2= H-, R_3 = Me-, Yield = 79 %,
Ar = C6H5-, 4-Cl-C_6H_4-, 4-(OMe)-C_6H_4-, 2-Cl-C_6H_4-, 3-Cl-C_6H_4-, 4-Br-C_6H_4-, 4-(OH)-C_6H_4-, 2-(NO_2)-C_6H_4-, 3-(OH)-4-(OMe)-C_6H_3-, 4-(OH)-3-(OMe)-C_6H_3-, 3,4-di-(OMe)-C_6H_3, 3-(OH)-C_6H_4-, 3,4,5-tri-(OMe)-C_6H_2-, 4-(NMe_2)-C_6H_4-, 3-(NO_2)-C_6H_4-, 4-(NO_2)-C_6H_4-, Furan-2-yl-, Thiophene-2-yl-
(**11/11a** = 4 mmol, **28** = 4 mmol, **12** = 4 mmol, **1** = 4 mmol)

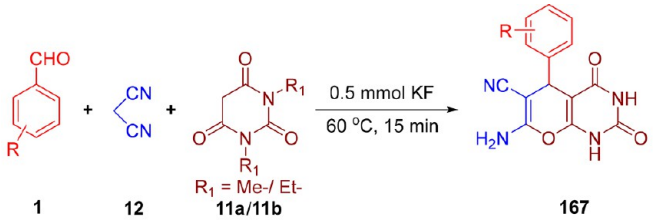
Scheme 113. Iron Ore Pellet-Promoted Synthesis of 166



1 12 11 166

Product 166: Yield = 73-93 %, Total Entry = 14, Time = 8-30 min;
R = H-, 2-(OH)-, 4-(NMe_2)-, 2-(OMe)-, 4-(OMe)-, 2,4-di-Cl-, 3,4,5-tri-(OMe)-, 4-(NO_2)-, 4-Cl-, 2,6-di-Cl-, 3-Me-, 2,4-di-(OMe)-, 4-Br-, 3-(NO_2)-
(**1** = 2 mmol, **12** = 2.2 mmol, **11** = 2 mmol)

Scheme 114. Potassium Fluoride-Catalyzed Synthesis of 167



1 12 11a/11b 167

Product 167: R_1 = Me-, Yield = 89-95 %, Total Entry = 8; R_2 = Et-, Yield = 89-92 %, Total Entry = 3;
R = H-, 4-F-, 2-Cl-, 4-Me-, 4-(OMe)-, 4-Cl-, 3-Br-, 4-(NO_2)-
(**1** = 5 mmol, **12** = 5 mmol, **11a/11b** = 5 mmol)

product was attained, but in this case, the time required is higher among all the other entries in Table 8. Comparatively lower yield of the product **162** was obtained when we used ILs, $[(DABCO)_2C_3H_5OH]\cdot 2Cl$, which required approximately 1 h to complete the reactions. The electronic nature of various EWG/ERG substituents on an aryl aldehydes did not considerably affect the isolated yield of the product for all the entries in Table 8.

Yu and Wang[211] utilized ILs, 1-^{n}butyl-3-methylimidazolium tetrafluoroborate ([BMIm]BF_4) or 1-butylpyridinium tetrafluoroborate ([BPy]BF_4) (1.5 g), with continuous stirring at 90 °C for 3 h to afford **164** (Scheme 111). The product was formed by two-component treatment of phenylmethylidenemalononitrile **163** with **11**. At the point of termination, a pale yellow crude solid of **164** was recrystallized using the solvent mixture of water−DMF. The overall yield of product **164** was not affected to any measurable way by the presence of any type of substituents. This reaction involved two component reaction only.

An effective and recyclable DES, made from choline chloride/Urea (20 mol %), was used by Tipale et al.[212] to afford pyrazolopyranopyrimidines **165** by treating **11**/**11a** (4

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mmol), **28**/**28a** (4 mmol), **12** (4 mmol) and derivatives, and **1** (4 mmol) at 80 °C in ethanol (Scheme 112). The DES was recovered by evaporation of aqueous ethanol and used up to two simultaneous runs. All the aryl and heteryl aldehydes reacted successfully and gave higher yield of **165**.

3.7. Miscellaneous Catalysts. Enayatollah et al.[213] described the synthesis of **166** through reaction of diversified aryl aldehydes **1** (2 mmol) with **12** (2 mmol) and **11** (2 mmol) utilizing iron ore pellet in aqueous ethanol under reflux (Scheme 113). After completion, the catalyst was separated from the product and reused up to six runs. The pure isolated yield of **166** was recrystallized from ethanol. The position and electronic nature of different substituents (EWG/ERG) on **1** did not affect the yield of **166** to any measurable quantity. The main benefit of this method was the use of iron ore pellets which is obtained naturally.

Elinson et al.[214] utilized potassium fluoride (0.5 mmol) as the catalyst to synthesize **167** with their respective analogues under solvent-free conditions via reaction of distinct aromatic aldehydes **1** (5 mmol) with **12** (5 mmol) and **11a**/**11b** (5 mmol) at 60 °C (Scheme 114). This method did not require the crystallization step. The presence of ERGs or EWGs on an aromatic ring of aryl aldehyde **1** did not significantly affect the yield of isolated product **167**.

4. CONCLUSION

Owing to the consequences of robust research, a wide literature has been accumulated over the past decades. This review is an attempt to revise the literature of diversified synthetic pathways for the fused heterocycles, 5*H*-pyrano[2,3-*d*]pyrimidine-mono,di,trione (thione) scaffolds and is completely based on different synthetic routes using different catalysts. 4-aryloctahydropyrano/hexahydrofuro[2,3-*d*]-pyrimidin-2-ones (thiones) **TS-1** synthesized through MCRs of diversified aryl aldehydes, urea/thiourea and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran or THF or THP using hybrid catalysts such as organocatalysts, green solvent, metal catalysts and ionic liquids as a catalyst. We found that, very few reports are there to synthesize **TS-1.** So, we have more chances to develop new synthetic methodologies for synthesis of derivatives of **TS-1**. However, 5-aryl-substituted pyrano[2,3-*d*]pyrimidinedione (triones)/(2-thiones) were synthesized through single-pot MCRs of diversified aryl/heteryl aldehydes or isatin with barbituric acid derivatives and an active methylene group containing malononitrile derivatives or curcumin, Meldrum's acid, alkyne, dimedone, *β*-naphthol, 4-hydroxycoumarin, or alkyne nitrile using hybrid catalysts such as NPs, organocatalysts, metal catalyst, ILs, miscellaneous catalysts, green solvent, and catalyst-/solvent-free synthesis. Most of the reactions gave a higher to excellent yield of 5-aryl-substituted pyrano[2,3-*d*]pyrimidinedione (triones)/2-thiones. Ionic-liquid-promoted synthesis of **TS-2** gave the highest yield among the others. Most of the strategies that are covered in this review paper are based on conventional and nonconventional methods, i.e., conventional heating, visible light, microwave, and sonication as well as electrolysis methods. It is hoped that this review will be helpful to the scientific community, synthetic organic chemists in academia as well as in industry to develop novel derivatives of 5*H*-pyrano[2,3-*d*]pyrimidine-2-ones (2-thiones)/ 2,4-diones (triones) scaffolds using greener, ecofriendly, and environmentally benign routes. These newly synthesized derivatives of targeted scaffolds **1** and **2** may show good biological activity and other applications.

AUTHOR INFORMATION

Corresponding Author

Hitendra M. Patel − *Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388 120 Gujarat, India;* orcid.org/0000-0003-4740-7329; Email: hm_patel@spuvvn.edu

Authors

Mehul P. Parmar − *Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388 120 Gujarat, India;* orcid.org/0000-0001-6958-8568

Ruturajsinh M. Vala − *Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388 120 Gujarat, India;* orcid.org/0000-0002-9829-1816

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.2c05349

Author Contributions

Mehul P. Parmar, Ruturajsinh M. Vala, and Hitendra M. Patel designed a review article collection. All authors contributed equally to the drafting.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

TS, targeted scaffold; TFA, trifluoroacetic acid; DMF, *N*,*N*-dimethylformamide; ERG, electron-releasing group; EWG, electron-withdrawing group; 3-CR, three-component reaction; *p*-TsOH = *p*-TSA, *para*-toluene sulfonic acid; IL, ionic liquid; MNPs, magnetic nanoparticles; RT, room temperature; MWI, microwave irradiation; TCCA, trichloroisocyanuric acid; AcOH, acetic acid; DBA, dibutyl amine; DABCO, 1,4-diazabicyclo[2.2.2]octane; GO, graphene oxide; DES, deep eutectic solvent; ChCl, choline chloride; DMSO, dimethyl sulfoxide; HDA, hetero-Diels−Alder; USI, ultrasound irradiation; PEG, polyethylene glycol; MW, magnetized water; MDW, magnetic deionized water; THF, tetrahydrofuran; THP, tetrahydro-2*H*-pyran

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