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Recent Advances in the Synthesis of Tetraketones *via* Multi-Component Reaction

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Abstract:
Tetraketones are one of the significant classes of oxygen containing organic compounds in the area of synthetic organic chemistry because of their various biological applications. Till now, many pathways were suggested by the researchers to achieve the targeted compounds but multi-component reactions are efficient and environment benevolent methods for preparation of several type of bioactive tetraketones. In this report affords have been made to collect the recent literature that describes the present status of tetraketones synthesis via multi-component reactions.

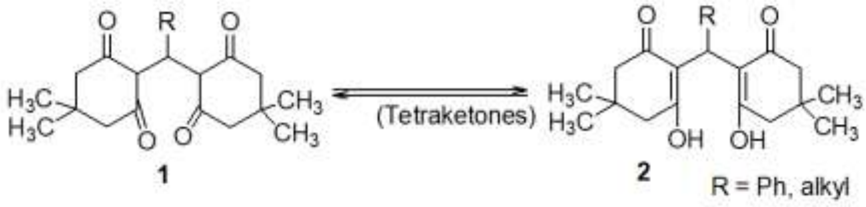
Keywords: Multi-component Reaction, Tetraketones, Green Chemistry, Dimedone, Active Methylene Compound

Introduction:

Multi-component reactions, which are also known as the multi-component assembly process (MCAP), are fast becoming one of the frontiers of organic synthesis, as they address both the diversity and complexity in organic transformations. In MCR, the condensation of three or more than three components without introduction of the poisonous intermediate in the atmosphere take place in such a way that the product contains a notable portion of atoms got from the entirety of the beginning material [1]. For combinatorial synthesis [2] and diversity-oriented synthesis [3] purpose MCR are preferred, as they have advantageous properties of lessening the production of hazardous waste material, lessening reactions steps, and human labour expenditure also get reduced. Multicomponent reactions (MCR) represent an excellent tool for the generation of small molecule compound libraries and are indispensable for structure-activity relationship (SAR) studies [4]. MCR chemistry due to its attractive attributes of high selectivity, high atomic efficacy, simple operation, saving time and energy contributes to sustainable chemical synthesis [5]. Many of the MCRs show their numerous applications in the field of drug discovery programme and medicinal chemistry [6, 7], synthesis of natural products [8], agro chemistry [9] polymer chemistry [10] and combinatorial chemistry [11]. Hence, MCRs plays a significant function in different examination fields like biomedical, synthetic organic, industrial chemistry and so forth.

Firstly, Laurent and Gerhardt in 1838 [12] observed the multicomponent synthesis of insoluble product benzoylazotide from almond oil and ammonia. After that Strecker in 1850 reported the primary MCR synthesis of α-amino cyanides [13]. After that many researchers made contributions to MCRs chemistry *via* discovery of important reactions. Till now hundreds of famous naming multicomponent reactions are discovered by various researchers. Out of them Hantzsch synthesis of dihydropyridine [14], Radziszewski synthesis of Imidazole [15], Hantzsch synthesis of Pyrrole [16], Biginelli synthesis of dihydropyrimidine [17], Huisgen reaction for synthesis of 5-membered (hetero)cycles [18], Mannich reaction for preparation of β-amino-carbonyl compound [19], Robinson's synthesis of tropinone [20], Asinger reaction for synthesis of thiazolidine [21], Passerini Reaction for synthesis of a-acyloxy amides [22], Kabachnik-Fields reaction for preparation of a-aminophosphonates [23], Petasis reaction for synthesis of substituted amines [24], Gewald reaction for preparation of substituted 2-aminothiophenes [25], Pictet Spengler reaction for synthesis of compound [26], Groebke-Blackburn-Bienayme (GBB) reaction for synthesis of fused nitrogen-containing aromatic compounds [27, 28], Povarov reaction for synthesis of quinoline [29], Bucherer-Bergs synthesis of hydantoin [30], Ugi reaction for synthesis of α-aminoacyl amide [31], Reppe carbonylation reaction for synthesis of carboxylicacids and derivatives [32], Knoevenagel Condensation [33] are well known. Basically, multicomponent reactions are the condensation reactions, so product formed by these reactions contains majority of the atom of beginning material. As these are condensations reactions so with the formation of product, H_2O and CO_2 are released as by-products. Using this synthetic MCRs route several other important compounds are prepared. Knoevengeal condensation products (with two different organic substrates attached to phenyl core) dicoumarol [34], tetraketone [35], [36], bis barbituric compound [37], bisindolylmethanes [38], bispyrimidines [39], and Pyrazole-Thiobarbituric Acid [40] are also prepared using this synthetic approach.

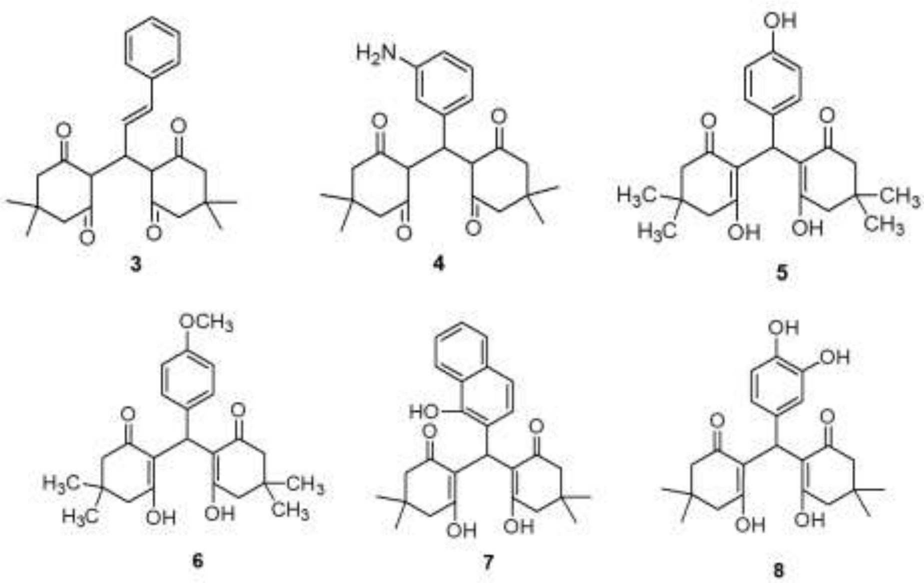
One of the significant class of oxygen containing organic compounds is 2,2′-Arylmethylene bis (3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) which is also known as tetraketone are used as key intermediates for organic preaparation of important heterocyclic compounds. Tetraketones is used as a precursor for therapeutic and biological activities possessing organic compounds such as acridindiones [41], xanthenes [42], and thioxanthenes [43]. Tetraketone **1** are present in tautomeric forms **2** which are in equilibrium with each other.



Scheme 1 Tautomerisation of Tetraketone

Tetraketones have sparked a lot of attention due to their several advantageous properties in pharmacy, biology and material science. These important bioactive compounds exhibit various biological and therapeutic activities; they show important enzyme inhibition activities such as inhibition effect on protein kinase [44], inhibitory effect on lipoxygenase [45], inhibitory effect on tyrosinase [46] along with that they also possess antibacterial [47] antiviral [48] and antioxidant activities [49]. Furthermore, Tetraketones due to their strong antioxidative activity [49], have gained interest as therapeutically agents against inflammation [50], asthma [51] and cancer [52]. They also show numerous applications in laser technology. [45,46].

Tetraketones shows lipoxygenase inhibiting [53, 45], tyrosinase inhibiting [46], antioxidant properties [45]. Compound **3** exhibit lipoxygenase inhibiting activity, (IC_{50}=7.8 µM) and it also show antioxidant activity (IC_{50}= 33.6 µM). Among compounds **3** and **4** higher tyrosinase activity is shown by compound **3** (IC_{50}= 2.06 µM) [88]. Moreover, compound **4** can be used as antifungi drug [54]. Compound **5** and **6** also possess activities like lipoxygenase inhibition [55]. They are used as a remedial source for Inflammation, Asthma due to their lipoxygenase inhibition activity. The cyctotoxic, antimicrobial, and antifungal activities are shown by tetraketones derivatives **7** and **8** [56]. Among these two compounds higher antioxidant activity shown by compound **8** with FRAP = (50 469.44 µmol L^{-1} Fe^{2+}), (IC_{50} = 0.0156µM). On the other hand, compound **7** showed better result for antifungal and antimicrobial activities. In case of cytotoxic result, compound **7** possess high cytotoxic activity.

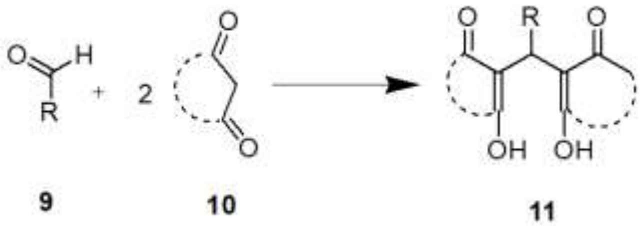


Scheme 2 Biologically active tetraketone derivative

Emphasising our interest on MCRs synthesized tetraketones molecules, so in present text we discuss about different catalytic methodologies following MCRs route for tetraketone preparation. As discussed earlier from biological point of view, these compounds show several applications. So, for preparation of these biologically active compounds a literature survey of three years is carried out in this review.

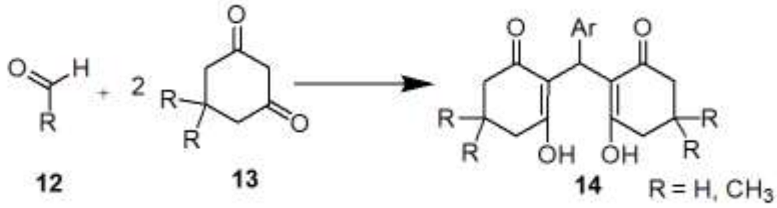
Review of literature:

Condensation reaction of various active methylene compounds with aromatic aldehydes to generate synthetic and biologically active compounds has sparked attention of several analysts in past years. Various Knoevenagel condensation reaction of reactive methylene compounds **10** (ethylacetoacetate, dimedone) or aldehydes **9** to give product **11** has been accomplished by using $CeZrO_4$ catalyst [57], Lewis acid complex $TiCl_4$ [58] Montmorillonite K10 [59], [Cu-MOF] modified chitosan [60] Amino acid amide (IL)[61], (FeNPs/Am@rGO)[62], $HoCrO_4$ [63], deep eutectic solvent $[CholineCl][ZnCl_2]_3$ [64], $Ga_4B_2O_9$ Lewis-base[65].



Scheme 3. Condensation of aldehyde with active methylene compound

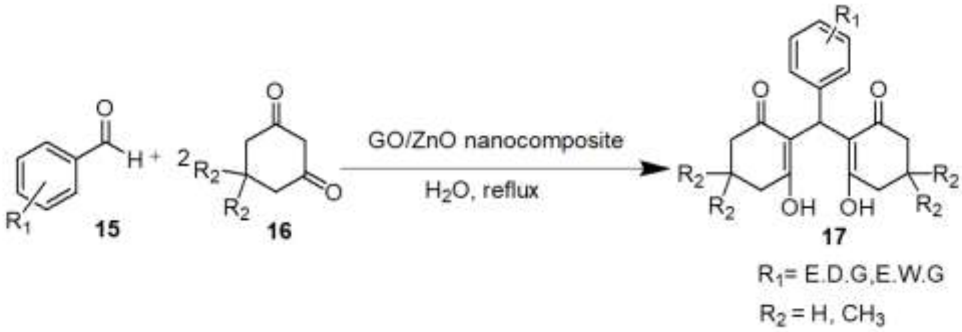
Initially, tetraketones were firstly reported in 1894 by Merling during synthesis of cyclohexane -1,3-dione from resorcinol [66]. Then, in 1899 practical synthesis of tetraketone was reported by Vorlander and Kalkow [67]. Primarily, also the traditional strategy of using piperidine [68], NaOH under effect of ultrasound radiation [69] and urea under effect of ultrasound radiation [70] for synthesis of tetraketone had also been reported. But these old strategies possess drawbacks of its catalyst recycling and also, they are not suitable for large scale production of product. One of the simplest and advantageous strategies for preparation of tetraketone **14** is the condensation of dimedone **13** with aldehyde **12**.



Scheme 4. Knoevenagel condensation of dimedone with aldehyde.

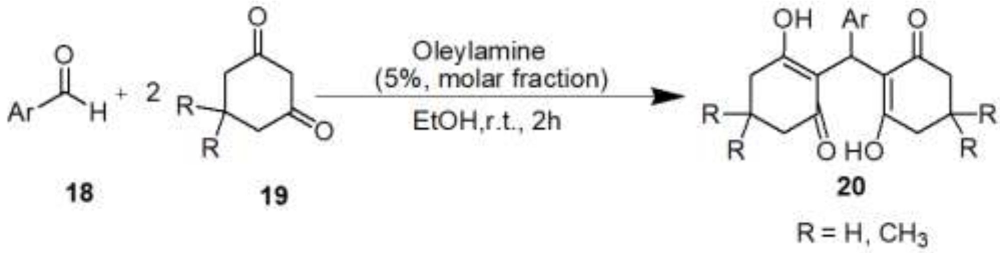
The two dimedone molecules hanged with the help of single aldehyde units is widely explored research area in synthetic organic chemistry. So in past years various researchers had reported synthesis of tetraketones by applying several methods which include TEBA triethylbenzyl ammonium chloride [71], KF/Al_2O_3 [72], alumina–sulfuric acid [73], $Yb(OTf)_3$–SiO_2 [74], $HClO_4$–SiO_2 [75], mesoporous silica nanoparticles (MSN)- adsorbed HBF_4 [76], taurine [77], copper nanoparticles supported onto silica [78], $SmCl_3$ [79], Fe^{3+}-montmorillonite [80], HY zeolite [81], nano-Fe/NaY [82], Ce-impregnated-MCM-41 [83] and $CoFe_2O_4$ [84], EDDA [85], Al/MCM-41 [86], choline chloride [87], PVP-stabilized Ni NPs [88], l-histidine in IL [89], silica-diphenic acid [90], Pd(0) nanoparticles [91], Ni(0) nanoparticles anchored on acid-activated montmorillonite [92], sodium docecylsulfate (SDS) [93], ([BMIm]BF_4-LiCl) [94], amino-appended b-cyclodextrins (ACDs) [95], water [96], [97], [98], Hexaflouro-2-propanol [99], nano Zn (Al2O4) [100], Fe3O4@SiO_2-SO_3H [101], tetrabutylammonium hydrogen sulphate Karade, [102], MnO_2NPs [103], Nano SiO_2Benzyltriethylammoniumchloride (Tebac) [104], Amano lipase DF [105], and Copper Octoate [106]. In our context we reported latest literature of last three year on tetra ketone synthesis using different catalyst.

Banakar *et al.* in 2018 [107] synthesized tetraketone **17** from condensation reaction of aldehyde **15** with 1, 3-dicarbonyl compounds **16** using nanocatalyst (GO/ZnO) in water under refluxing. This process efficiently produces tetraketones in good to excellent yield from 60-99%.



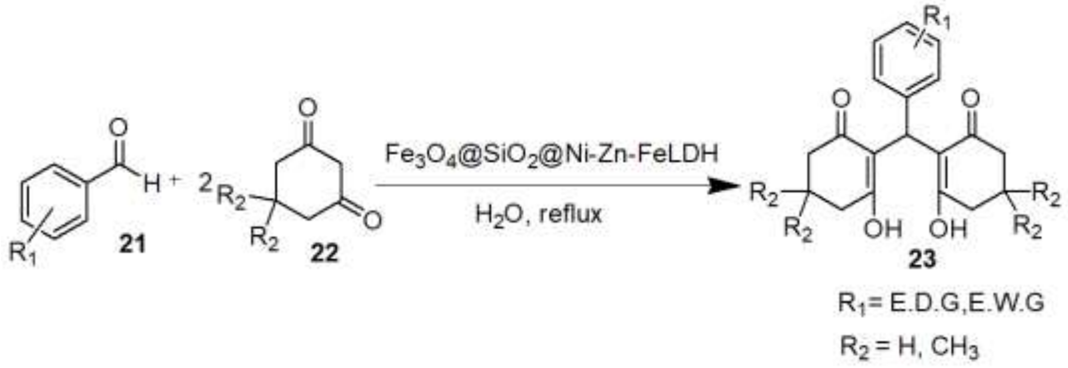
Scheme 5. Synthesis of tetraketone using nano catalyst (GO/ZnO)

Xinwei *et al.* in 2018 [108] investigated oleylamine catalysed preparation of Tetraketones **20** *via* a reaction of dimedone **19** and aldehyde **18** in ethanol at room temperature. On substituting variety of aldehyde aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring in Ar position products yield from 78-93% is obtained.



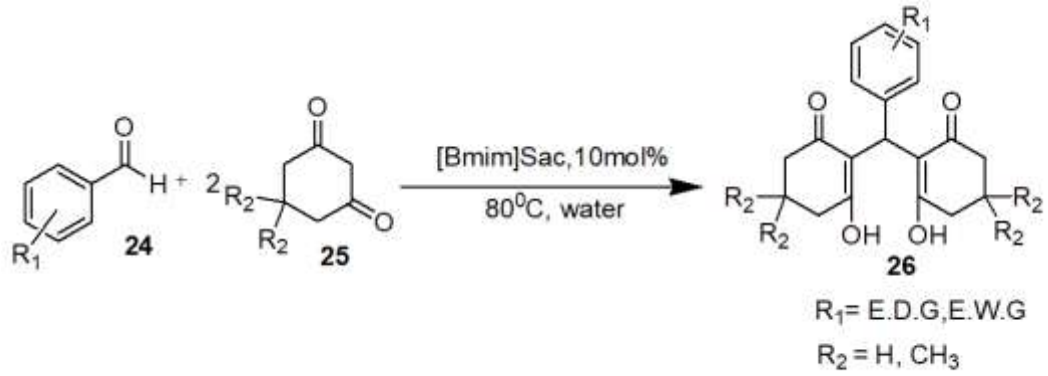
Scheme 6. Oleylamine based synthesis of tetraketone

Gilanizadeh *et al.* in 2018 [109] reported the preparation of tetraketone **23** by a reaction of aldehyde **21** and 1,3-dicarbonyl compounds **22** catalysed by 17 to 36 nm sized novel magnetic Fe_3O_4@SiO_2@Ni-Zn-Fe layered double hydroxide (LDH) in presence of water under refluxing condition. On substituting variety of aldehyde with aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene in R_1 position product yield from 89-96% is obtained.



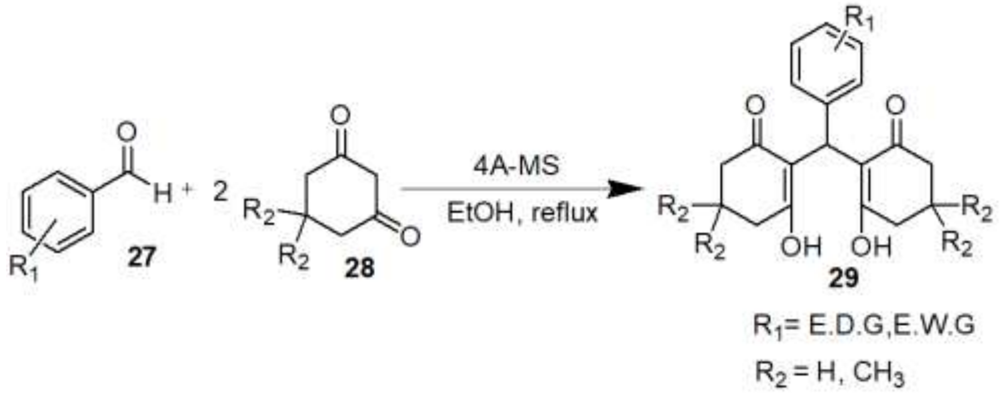
Scheme 7. Synthesis of tetraketone using nano Fe_3O_4@SiO_2@Ni-Zn-Fe

Sharma *et al.* in 2019 [110] investigated an efficient synthesis of Tetraketones **26** from dimedone **25** and aldehyde **24** using anion-functionalized ionic liquid [Bmim]Sac in water at ambient temperature. Several aldehydes with aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring in R_1 position reacts with 1,3-dicarbonyl compounds to give yield from 82-92% in less interval of time.



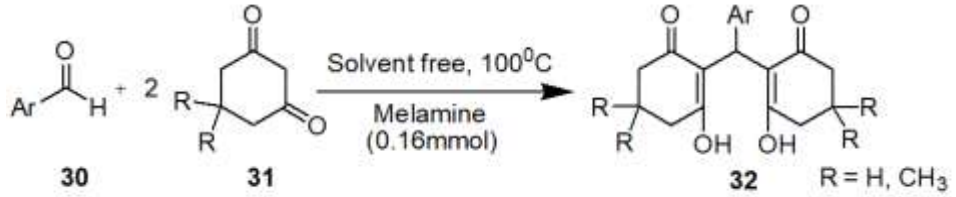
Scheme 8. Synthesis of tetraketone using [Bmim]Sac

Magyar *et al.* in 2019 [111] reported 4 Å molecular sieves as advantageous catalyst for preparation of tetraketone **29** using dimedone **28** and aldehydes **27** in ethanol under refluxing. The products acquired using these methodologies are in excellent yield from 90-99%. The attractive key features of this catalyst are that it is easily accessible, low cost, can be reobtained-reused without any noticeable loss in its effectiveness.



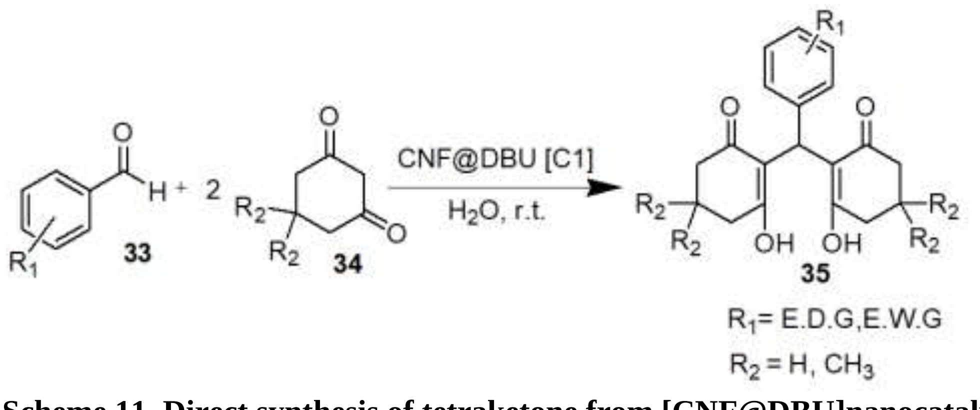
Scheme 9. 4 Å molecular sieves-based synthesis of tetraketone

Kamali *et al.* in 2019 [112] used melamine to catalysing reaction of aldehydes **30** and 1,3-dicarbonyl compounds **31** in solvent free condition for synthesis of tetraketone **32**. This efficient strategy affords tetraketones **32** in excellent yield from 90-98%. This procedure used for synthesis of tetraketone **32** was simple, time saving and environment benevolent.



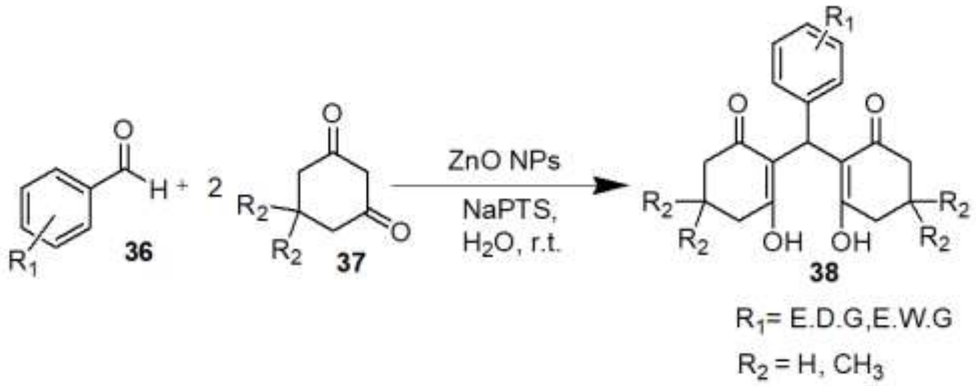
Scheme 10. Tetraketone synthesis from melamine

Lasemi *et al.* in 2020 [113] reported that tetraketone **35** can be prepared *via* reaction of dimedone **34** and aldehyde **33** catalysed by 30-60 nm sized nanocatalyst *i.e.* [CNF@DBU] at room temperature. In this strategy a wide variety of aldehyde with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring in R_1 position reacts with 1,3-dicarbonyl compounds in water to give yield from 30%-97%.



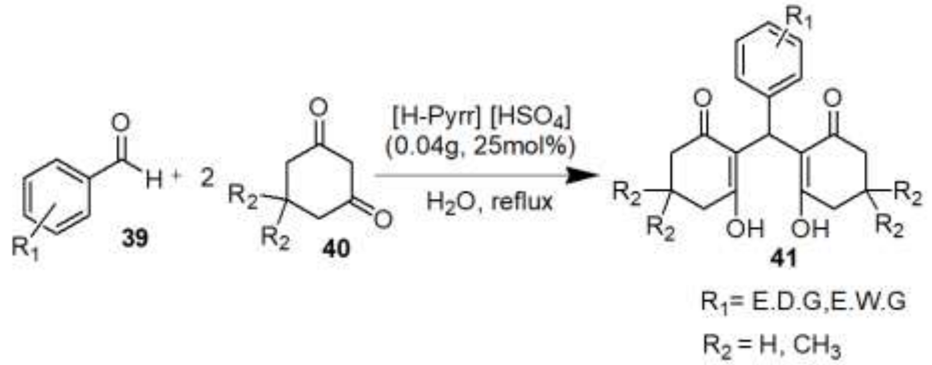
Scheme 11. Direct synthesis of tetraketone from [CNF@DBU]nanocatalyst:

Attar *et al.* in 2020 [114] worked on the synthesis of tetraketone **38** using 45-56nm sized bio-fabricated ZnO NPs as catalyst. This efficient catalyst catalyses the reaction of aldehyde **36** with dimedone **37** in water at room temperature to give Tetraketones **38** in good to excellent yield from 40- 95%. The attractive attributes of this strategy are that this catalyst is easily accessible, low cost, easy work-up, shorter reaction times, environment benevolent reaction condition, safety and great yields.



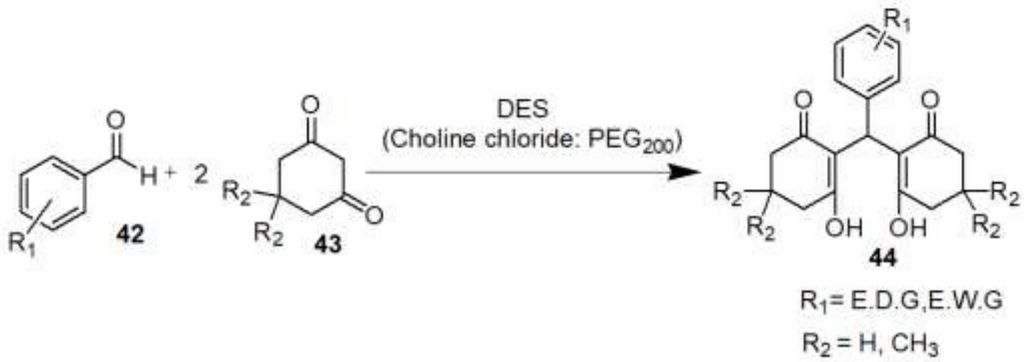
Scheme 12. ZnO NPs initiated synthesis of tetraketone

Zabihzadeh *et al.* in 2020 [115] reported a convenient synthesis of Tetraketones **41** from the reaction of dimedone **40** with aldehydes **39** using Pyrrolidin-1-ium hydrogen sulfate ([H-Pyrr][HSO_4]) in water under refluxing at room temperature. The products yield acquired using this efficient procedure are excellent from 40- 95% on substitution of different aldehyde with 1,3-dicarbonyl compounds.



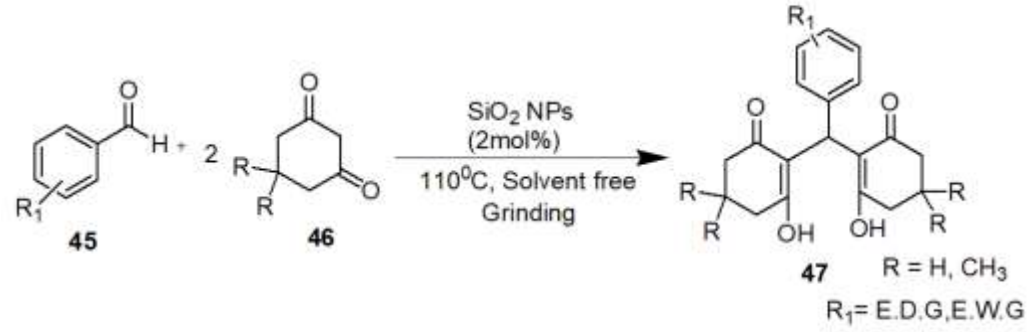
Scheme 13. Synthesis of tetraketone using ([H-Pyrr][HSO_4])

Srivastava *et al.* in 2020 [116] reported that tetraketone **44** can be prepared *via* reaction of dimedone **43** and aldehyde **42** catalysed by choline chloride: PEG based deep Eutectic mixture. Several aldehydes with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring reacts with 1, 3-dicarbonyl compounds to give yield from 70-90%.



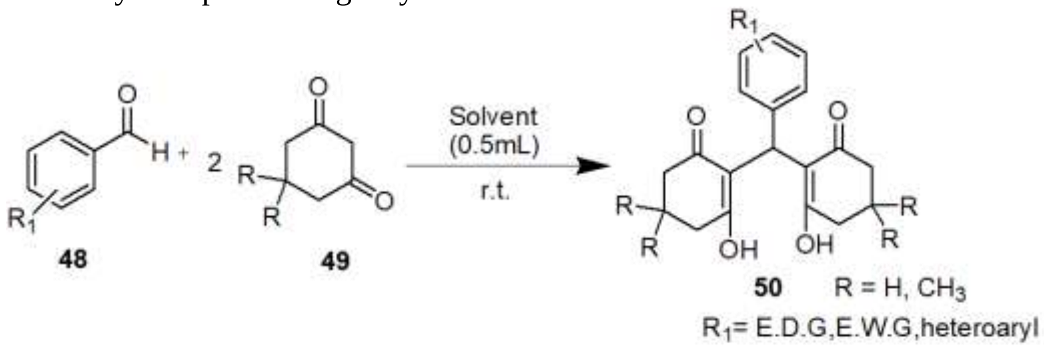
Scheme 14 Synthesis of tetraketone using DES

Alinezhad *et al.* in 2019 [117] reported tetraketone **47** are synthesized *via* reaction of dimedone **46** with aldehyde **45** using SiO_2 nanoparticles at room temperature. In this strategy a wide variety of aldehyde with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring reacts with 1,3-dicarbonyl compounds in solvent free conditions to give yield from 74-97%. The attractive attributes of this methodology are excellent yields, catalyst recyclability, solvent free conditions.



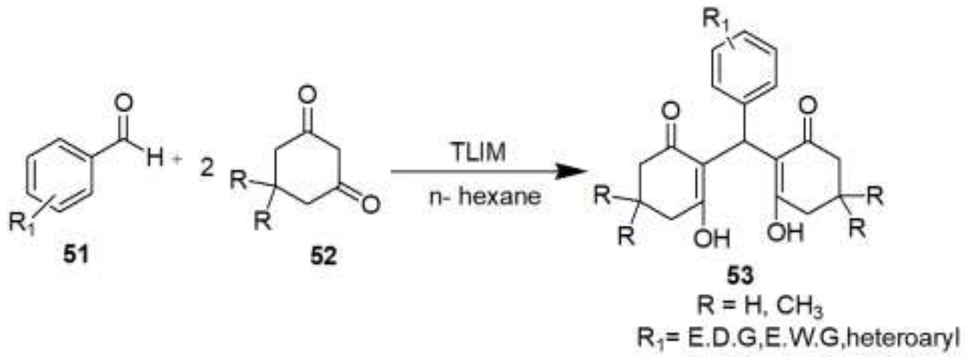
Scheme 15 SiO_2 initiated synthesis of tetraketone

Arora *et al.* in 2019 [36] reported tetraketone **50** can be prepared *via* reaction of dimedon **49** with aldehyde **48** in methanol at room temperature. A broad spectrum of aldehyde with aryl, and with electron withdrawing or releasing group attached to benzene ring reacts with 1,3-dicarbonyl compounds to give yield from 63- 89%.



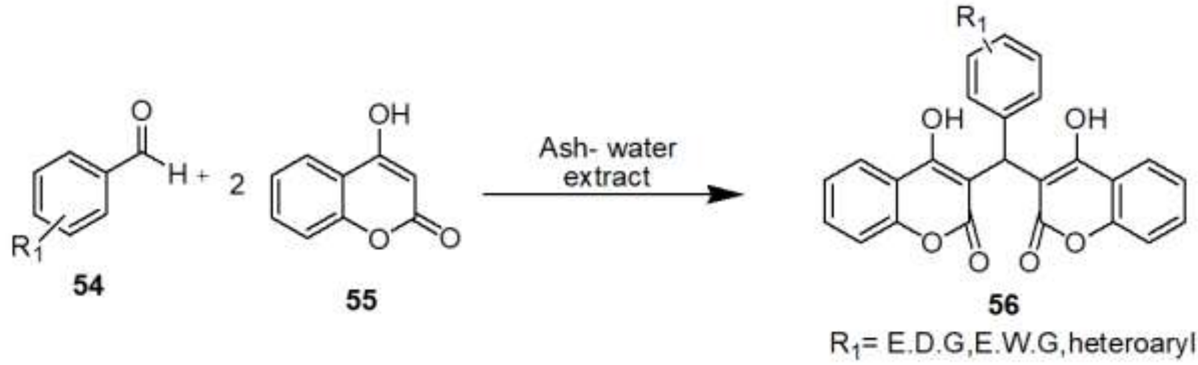
Scheme 16 Preparation of tetraketone in methanol

Fu *et al.* in 2018 [118] reported enzymatic strategy for tetraketone **53** that they can be prepared *via* reaction of dimedone **52** with aldehyde **51** catalysed by lipase TLIM in n-hexane at room temperature. In this strategy a wide variety of aldehyde with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring reacts with 1,3-dicarbonyl compounds to give yield from 74-97%.



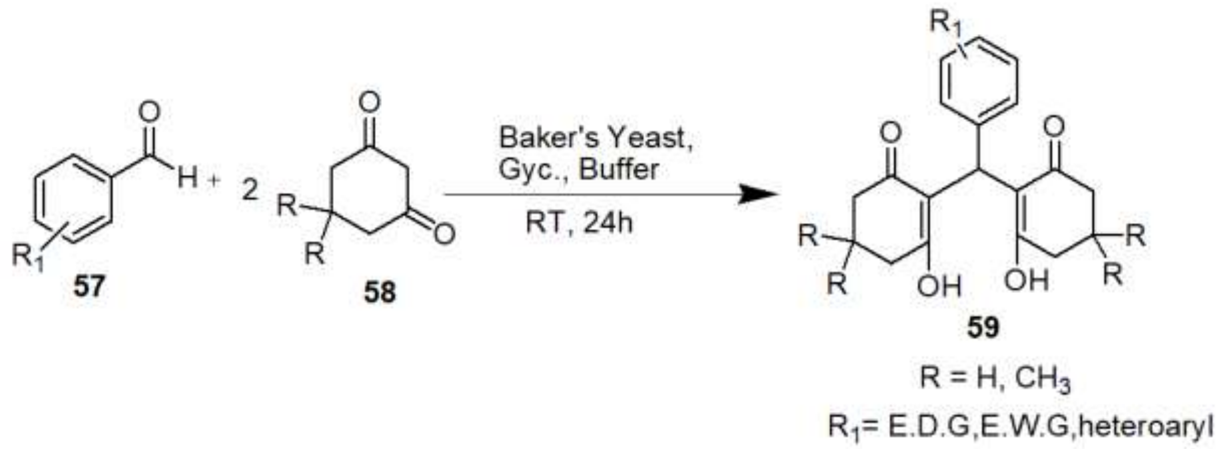
Scheme 17 TLIM based synthesis of tetraketone

Chia *et al.* in 2018 [119] reported that bis-enols **56** are synthesized *via* reaction of aldehydes **54** and 4-hydrocycoumarins **55** catalysed by waste onion peel ash water extract at 80^{0}C. In this method a broad spectrum of aldehyde with aryl, and with electron withdrawing or releasing group attached to benzene ring reacts with 4-hydrocycoumarins to give yield from 62-94%. The attractive key features of this strategy are that this catalyst is easily accessible, low cost, effective catalyst that can be reobtained-reused without any noticeable loss in its effectiveness, handling, ease of formation, product-purification, straightforward work-up, shorter reaction times, environment benevolent reaction condition, safety and great yields.



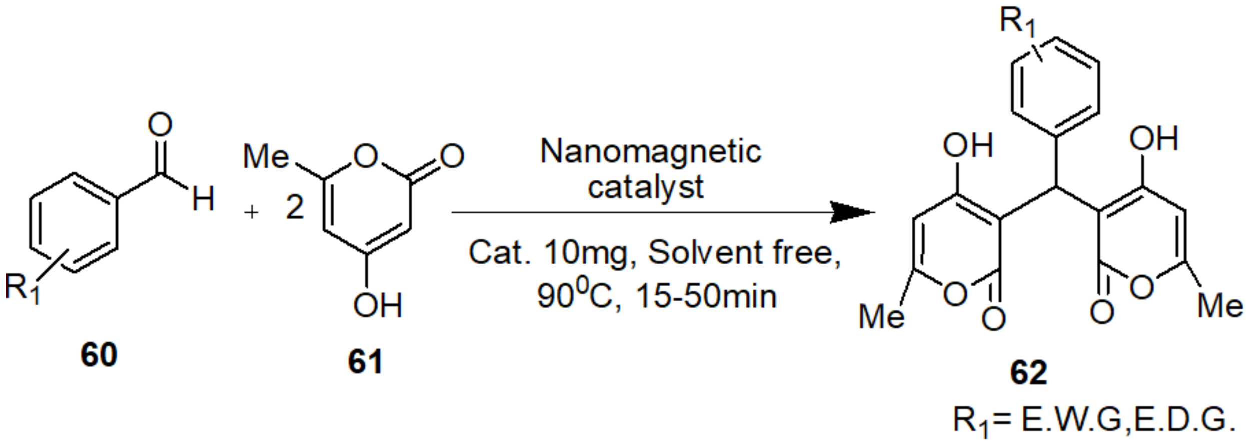
Scheme 18 Synthesis of tetraketone using onion peel ash water

Ashtarian *et al.* in 2019 [120] reported tetraketone **59** can be prepared *via* reaction of dimedone **58** and aldehyde **57** catalysed by fermenting yeast (obtained from solution of baker yeast, D-glucoses, phosphate-buffer) at room temperature. In this strategy a wide variety of aldehyde with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring reacts with 1,3-dicarbonyl compounds to give yield from 80- 95%.



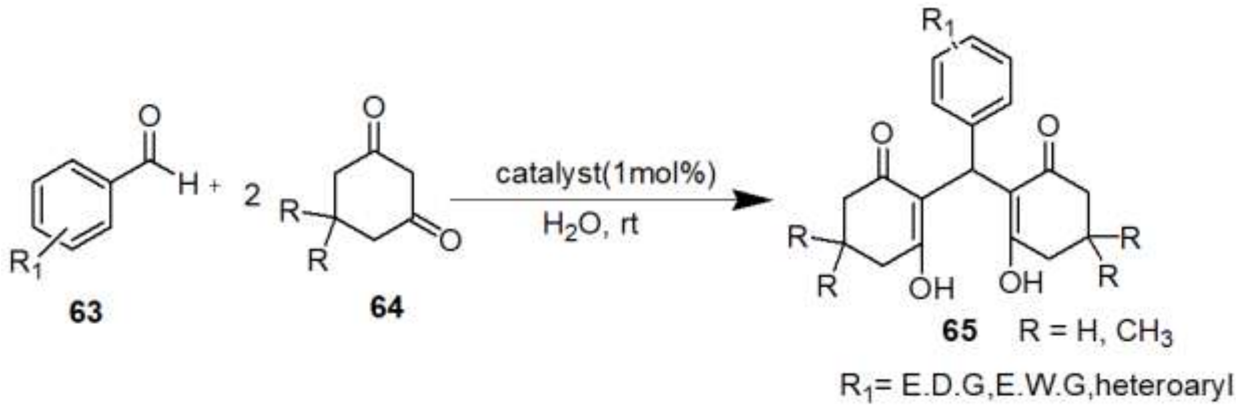
Scheme 19 Tetraketone synthesis using fermenting yeast

Mohammad Ali Zolfigol *et al.* in 2019 [121] investigated nanomagnetic $Fe_3O_4@SiO_2/(CH_2)_3$-[Imidazolium-SO_3H]C catalysed synthesis of tetraketone **62** through a reaction of aldehydes **60** with 4-hydroxy-6-methyl-2H-pyran-2-one **61** at 90^0C in solvent free conditions. Abroad spectrum of aldehyde with aryl, and with electron withdrawing or releasing group attached to benzene ring reacts with 1,3-dicarbonyl compounds to give yield from 82- 95%. The attractive key features of this strategy are great yield, such as low cost, easy accessibility and recyclability of catalyst, product purification, and environment benevolent.



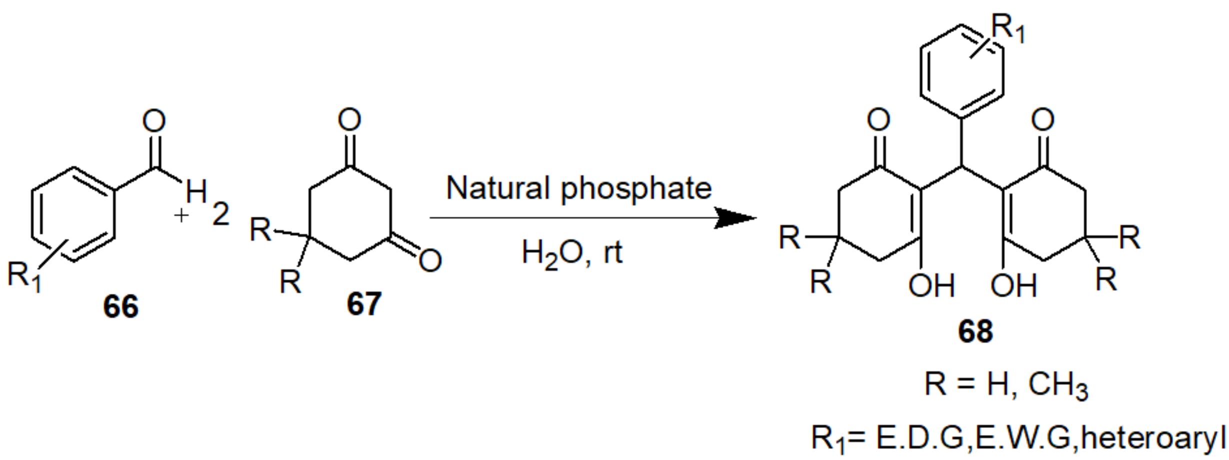
Scheme 20 Preparation of tetraketone using nanomagnetic catalyst

Halimehjani *et al.* in 2019 [122] have synthesized tetraketone **65** *via* a reaction of dimedone **64** with aldehyde **64** using tetracationic acidic organic salt based on DABCO. In this methodology a broad spectrum of aldehyde with aryl, and with electron withdrawing or releasing group attached to benzene ring reacts with 1,3-dicarbonyl compounds to give yield from 40%-98%.



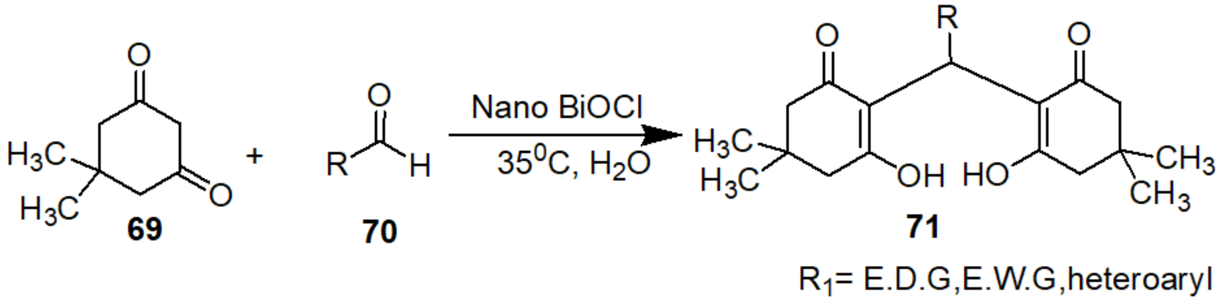
Scheme 21 Synthesis of tetraketone using tetracationic acidic organic salt

Fallah *et al.* in 2017 [123] reported that tetraketone **68** can be prepared *via* reaction of aldehydes **66,** 1, 3- cyclic dicarbonyl **67** catalysed by Natural phosphate in water and ethanol. In this strategy a wide variety of aldehyde with aryl, and with electron withdrawing or releasing group attached to benzene ring reacts with 1,3-dicarbonyl compounds to give yield from 90-100%.



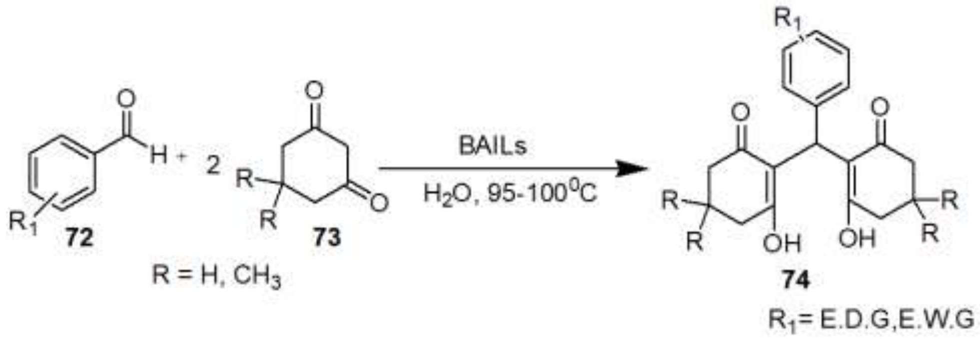
Scheme 22 Natural phosphate initiated tetraketone synthesis

Sapkal *et al.* in 2017 [124] reported a convenientand efficient, green protocol for the preparation of tetraketones **71** by using a reusable catalytic agent [BiOCl-NPs] [16]. This catalyst catalyzes the condensation reaction of dimedone **69** with aldehyde **70** in water under ultrasound irradiation. Important features of this method are great yield, product purity and mild conditions. On substituting various aryl or electron releasing or withdrawing group attached to benzene ring in R position product yield from 83-95% is obtained.



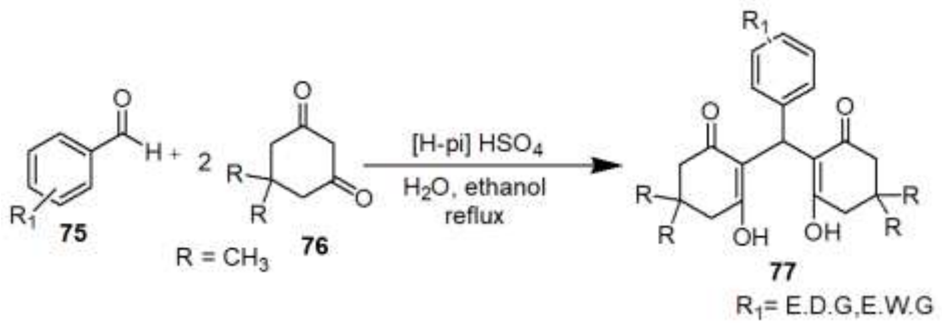
Scheme 23 [BiOCl-NPs] initiated synthesis of tetraketone

Ashtarian *et al.* in 2019 [125] reported tetraketone **74** are prepared by an efficient route of using (BAILs) as catalyst in a reaction of dimedone **73** with aldehyde **72**. This process is carried out in aqueous condition at room temperature. Product yield obtained through this procedure is excellent from 86-95%.



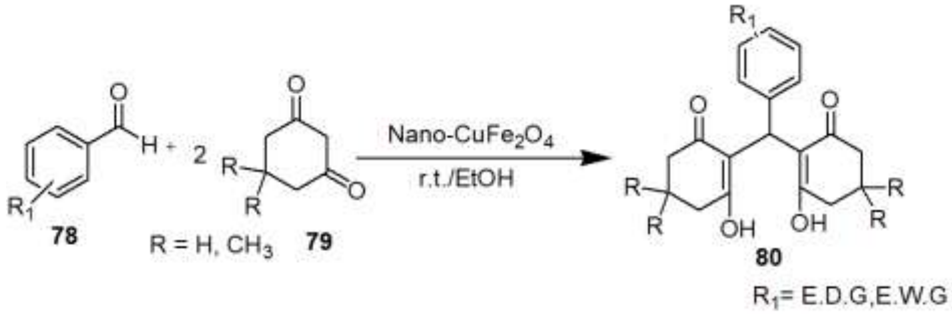
Scheme 24 Synthesis of tetraketone using (BAILs)

Jashani *et al.* in 2018 [126] reported tetraketone **77** can be prepared *via* reaction of aldehydes **75** and1,3-dicarbonyl compounds **76** catalysed by 1,4-Piperazinium Hydrogen Sulfate in ethanol, water. In this strategy a wide variety of aldehyde with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring reacts with 1, 3- dicarbonyl compounds to give yield from 91-98%. The attractive attributes of this methodology are mild reaction condition, great yield, use of inexpensive, easily recyclable and effective catalyst. The attractive attributes of this strategy are great yield, use of inexpensive, easily recyclable and effective catalyst.



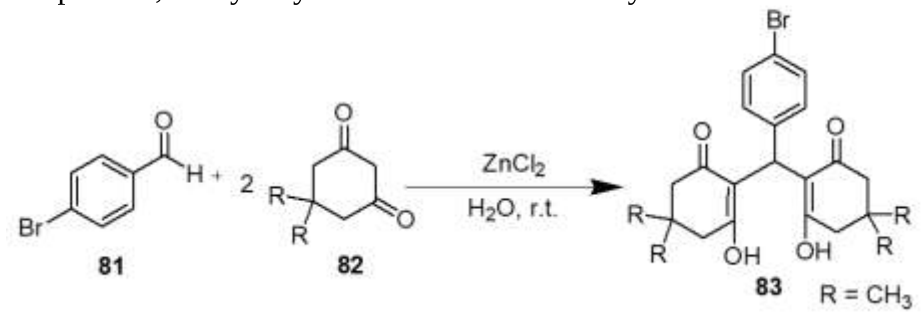
Scheme 25 Synthesis of tetraketone using 1,4-Piperazinium Hydrogen Sulfate

Vajar *et al.* in 2019 [127] used nanocatalyst $CuFe_2O_4$ for synthesis of tetraketone **80**. This efficient nanocatalyst catalyse reaction of aldehydes **78** and 1, 3- dicarbonyl compounds **79** in ethanol at room temperature. On substituting broad spectrum of aldehydes with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring in R_1 position products yield from 82-94% is obtained.



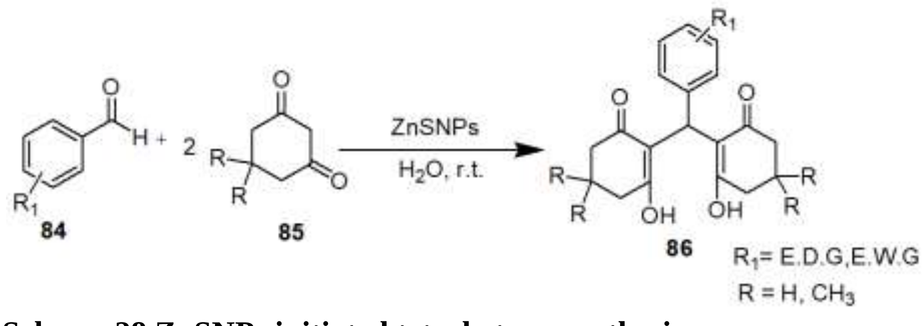
Scheme 26 $CuFe_2O_4$ initiated synthesis of tetraketone

Thamotharan *et al.* in 2018 [128] investigated that tetraketone **83** can be prepared *via* reaction of 4-bromoaldehyde **81** and1,3-dicarbonyl **82** compounds using $ZnCl_2$ at room temperature in water. The key highlights of this process are mild reaction condition, great yield, use of inexpensive, easily recyclable and effective catalyst.



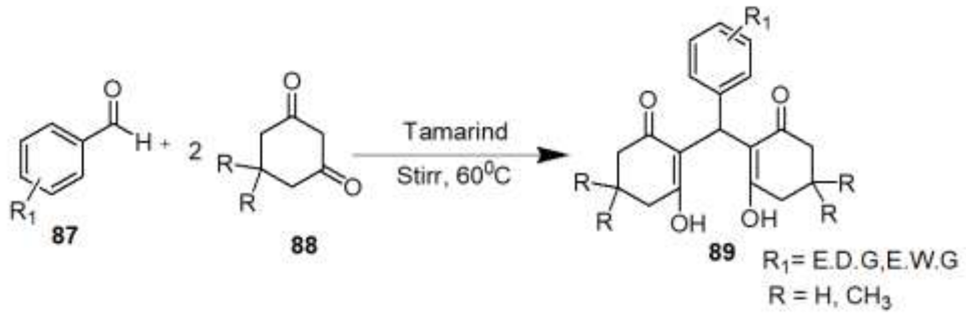
Scheme 27 Synthesis of tetraketone using $ZnCl_2$

Ghomi *et al.* in 2018 [129] reported tetraketone **86** can be prepared *via* reaction of dimedone **85** with aldehyde **84** and 1,3-dicarbonyl compounds **85** catalysed by ZnSNPs in water at room temperature. This efficient procedure gives excellent yield of tetraketones in less interval of time. The attractive attributes of this procedure are mild reaction condition, great yield, use of inexpensive, easily recyclable and effective catalyst.



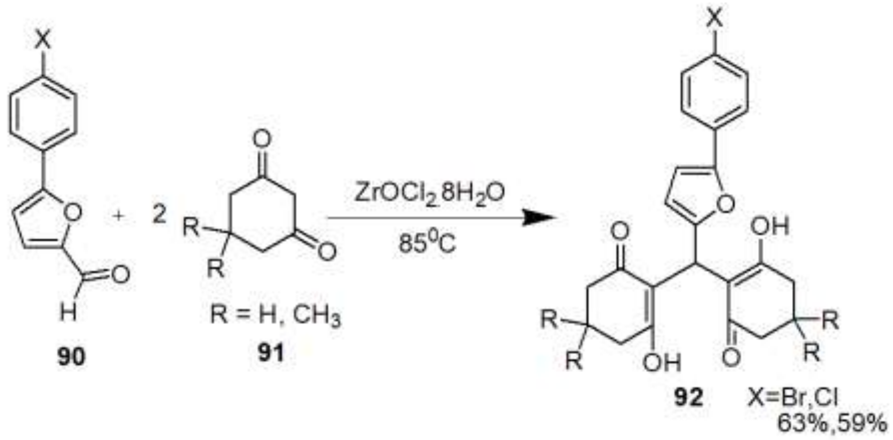
Scheme 28 ZnSNPs initiated tetraketone synthesis

Pal *et al.* in 2018 [130] developed an efficient route for synthesis of tetraketone **89** using tamarind as catalyst in reaction ofaldehydes **87** and1,3-dicarbonyl compounds **88** in water at 60^0C. In this strategy a wide variety of aldehyde with alkyl, aryl, heteroaryl and with electron withdrawing or releasing group attached to benzene ring reacts with 1, 3- dicarbonyl compounds to give yield from 85-98%.



Scheme 29 Synthesis of tetraketone using tamarind

Silva *et al.* in 2018 [131] reported tetraketone **92** can be prepared *via* reaction of dimedone **91** with aldehyde **90** catalysed zirconium ($ZrOCl_2$,$8H_2O$) at 85°C. The products in good to excellent yield are acquired using this methodology.



Scheme 30 ($ZrOCl_2$, $8H_2O$) catalysed synthesis of tetraketone

Conclusion:

Now days, multi-component reactions attract attention due its advantageous includes high yields, avoid harsh reaction conditions, avoid unwanted byproducts and decrease of the usage of hazardous chemicals. This short review article will help the beginners to study about synthesis of biologially important tetraketones *via* atom economy reactions.

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