



IMPORTANT ROLES OF CYCLIC DI-KETO COMPOUNDS TO ONE POT SYNTHESSES OF NITROGEN HETEROCYCLIC SYSTEMS

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Abstract: Methods for the construction of Heterocycles from cyclic diketo compounds such as dimedone, barbituric acid, tetronic acid, substituted 1,3-cyclohexadione, 1,3-indandione are discussed. It is shown that various diketo groups can be used as building blocks of quinoline derivatives. The synthesis having diketo compounds is really simple and environmentally benign. The key features of diketo reactions are the high yields of products, short reaction times and the use of various principles such as green synthesis, aqueous media, solvent free methods etc.

Keywords: Heterocyclic compounds, 1,3-indandione, multi-component reaction reviews, one pot synthesis, substituted 1,3-cyclohexadione, tetronic acid.

Introduction

Over the last ten years, diketo compounds have been used in many new developments of heterocyclic derivatives with high yields. One of the diketo namely, dimedone, which specifically traps sulfenic acids, has been used for synthesis of a novel group of compounds that diketo derivatives with reporter tags such as biotin for affinity capture and fluorescent labels for visual detection. These reagents allow identification of the cysteine sites and proteins that are sensitive to oxidation¹. Another diketo compounds such as tetronic acids are naturally occurring molecules with a variety of biological activities.² Earlier, synthesis of biologically active 3-acyl-5-methoxycarbonyl tetronic acids was reported by Mitsos *et. al.*³ A new strategy for the synthesis of functionalized tetronic acids was developed by Schobert and coworkers, applying the “domino” process, which comprises of the reaction between the esters of α -hydroxy acids and the cumulated phosphorus ylide ketenylidene triphenyl phosphorane.⁴ 1,3-indandione is an important member of class of 1,3-diketo compounds and literature is full of references giving its reactions with a variety of substrates yielding a wide range of compounds of pharmaceutical interest.⁵

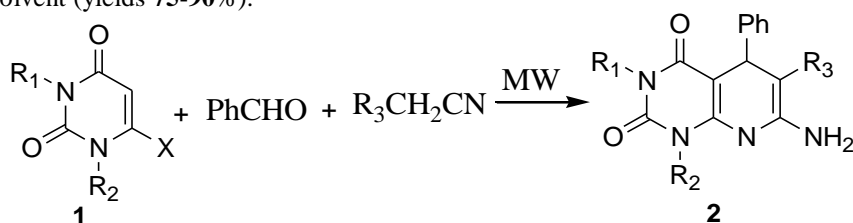
Multi component reactions (MCRs) is the one of the most important reactions in organic chemistry for the formation of carbon—carbon bonds and much effort has been involved to the development of this reactions in recent years.^{6,7} The nitrogen heterocycles and their derivatives represent a chief class of organic molecules which attract the interest of both synthetic and medicinal chemists.⁸ In addition to develop the new methods for MCRs, there have been an extreme interest in the selection of different catalysts.

Our contribution is a brief review to the knowledge about importance of di-keto compounds in multi component reactions concentrating with high yields. The review focus about the illustration of multi component reactions such as Biginelli⁹, Passerini¹⁰, Ugi¹¹ and Hantzsch¹² which provide a wide variety of important heterocycles. This Manuscript will assist to the chemist to have a glance on the significance of one pot syntheses.

DIKETO DERIVATIVES IN THE SYNTHESIS OF HETEROCYCLES

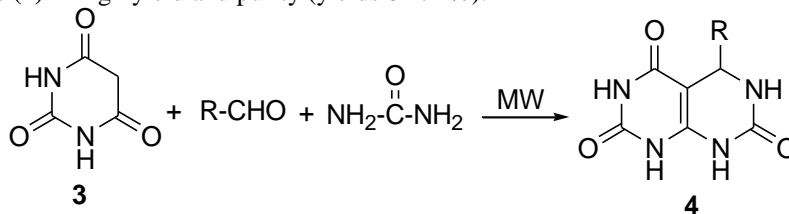
SCHEME 1

The diketo compounds(1) develop the highly expedient methods for the synthesis of annelated uracil libraries was reported a novel three component one-pot synthesis of well functionalized pyrano[2,3-*d*]pyrimidines (2) under microwave irradiation in the absence of catalyst and solvent (yields **75-90%**).¹³



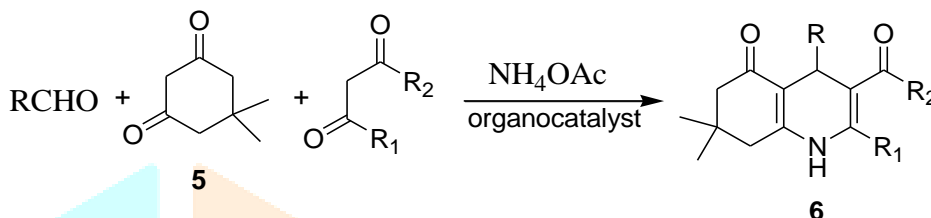
SCHEME 2

It should be noted that barbituric acid (**3**) has been played major role for the construction of heterocycles which are more important for pharmacological cyclic skeletons. A green approach to multicomponent reaction (MCR) protocol was explored by Mazaahir Kidwai *et al.* who have reported a simple, rapid and one-pot water-mediated procedure for the synthesis of pyrimido[4,5-*d*]pyrimidines (**4**) in high yield and purity (yields **82-92%**).¹⁴



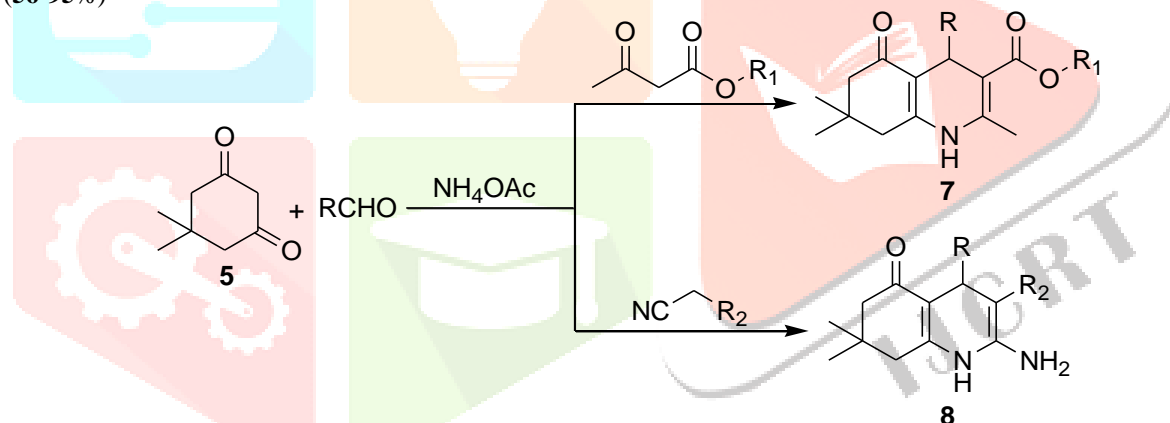
SCHEME 3

Kumar and Maurya demonstrated the synthesis of hexahydroquinolines (**6**) via a four-component unsymmetrical Hantzsch condensation using the diketo compound (**5**) with aryl aldehydes, acyclic *b*-dicarbonyl compounds and ammonium acetate at ambient temperature. Optimisation tests showed *L*-proline to be an efficient catalyst among others giving products (yields **47-79%**).¹⁵



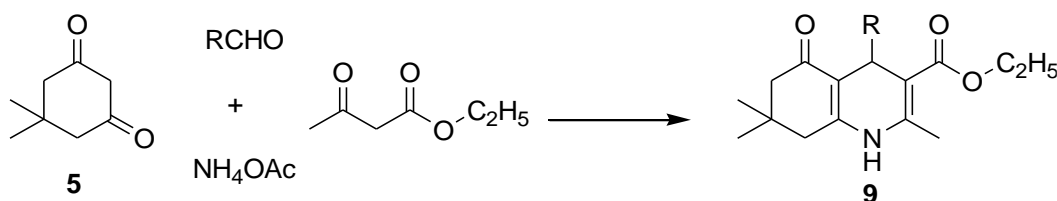
SCHEME 4

In another article, the progress of diketo compounds (**5**) with solvent free condition was reported to have growing the significance because of their high efficiency, operational simplicity and environmentally benign nature. The reactions were observed to follow the expected routes to yield 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexa-hydroquinolines (**7**) and 2-amino-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexa hydro quinoline-3-carboxylic acid ethyl ester (**8**) respectively with good to excellent yields (**56-95%**).¹⁶



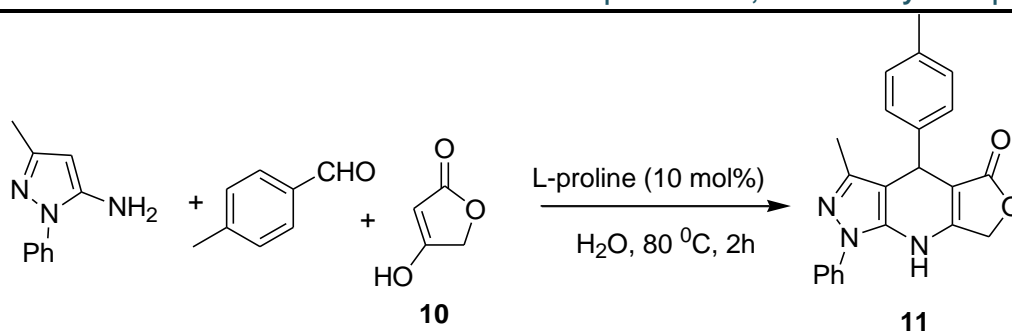
SCHEME 5

In this communication of diketo group, Bandgar *et al.* have reported a simple, efficient method for the one-pot synthesis of polyhydroquinoline derivatives (**9**) from dimedone (**5**) with ester, aldehyde and ammonium acetate in refluxing water (yields **90-99%**).¹⁷

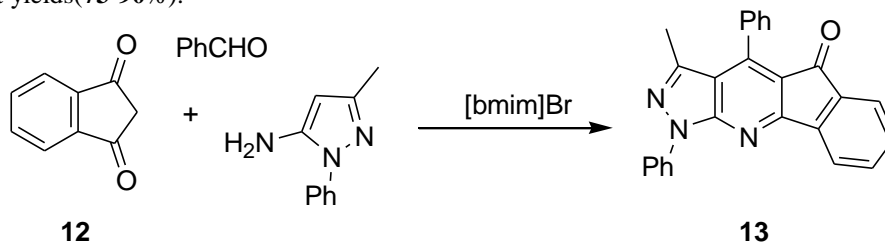


SCHEME 6

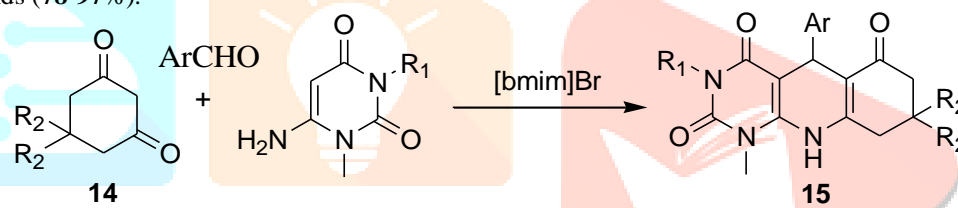
Ji *et al.*¹⁸ have used tetronic acid (or 1,3-indanedione) (**10**) to develop the pyrazole-fused 1,4-dihydropyridines (**11**) starting from 5-amino-1-phenyl-3-methylpyrazole, aldehyde (**5**) in the presence of *L*-proline. Although the solvent chosen was ethanol, this reaction proceeded also in water at 80 °C to provide the product in excellent yield (**90%**)

**SCHEME 7**

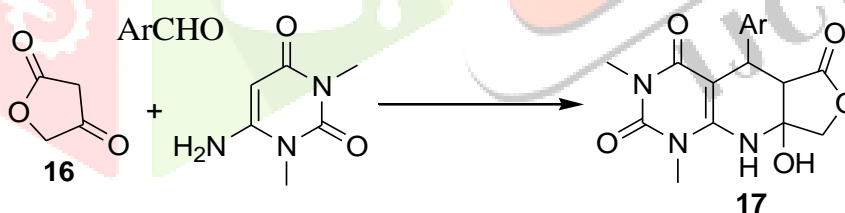
By using 1,3-dicarbonyl compound (**12**), aldehyde, 5-amino-3-methyl-1-phenylpyrazole under 1-butyl-3-methylimidazolium bromide ([bmim]Br) as the solvent and promoter, it was possible to obtain indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-5(1*H*)-one (**13**) derivatives in excellent yields (**73-90%**).¹⁹

**SCHEME 8**

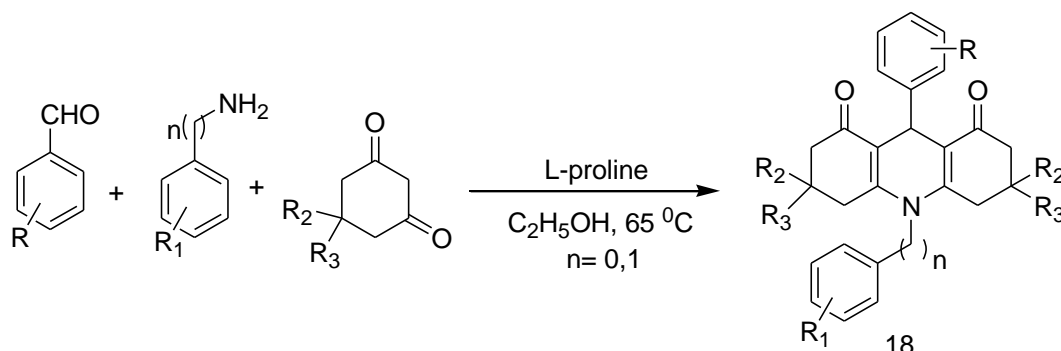
In above similar conditions, Shi, *et al.* used the same method, replacing 1,3-indandione with substituted 1,3-cyclohexadione (**14**) which yielded pyrimido[4,5-*b*]quinoline (**15**) derivatives from aromatic aldehydes and 6-amino-3-substituted-1-methyl-pyrimidine-2,4(1*H*, 3*H*)-diones. It was done through dimidone analogues derivatives in ionic liquid without any catalyst and found high yields (**78-97%**).²⁰

**SCHEME 9**

Using the diketone group, a comfortable method for the synthesis of furo-pyrido[2,3-*d*]pyrimidine (**17**) derivatives was developed *via* the three-component reaction of an aldehyde, tetronic acid (**16**) and 6-amino-1,3-dimethyl-pyrimidine-2,4-dione in aqueous media without the use of catalyst. This protocol it gave better yields (**77-91%**), convenient procedure and reduced environmental impact.²¹

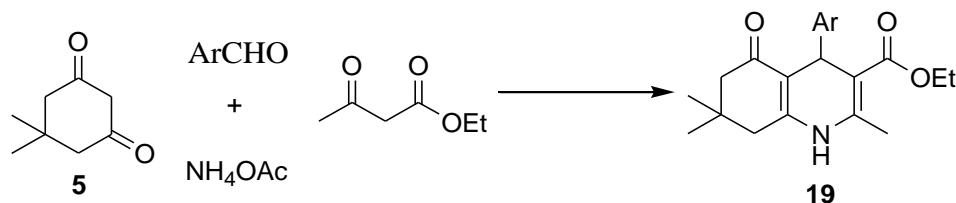
**SCHEME 10**

Proline-catalyzed diketone developed the synthesis of 1,8-dioxo-decahydroacridines (**18**) which was achieved by Venkatesan *et al* via one-pot, three-component condensation of aromatic aldehydes, cyclic diketone, and aryl amines in aqueous ethanol medium. This method offers the advantages of proceeding in neutral and mild conditions, giving high yields (**73-88 %**) of acridines with easy workup procedure²².

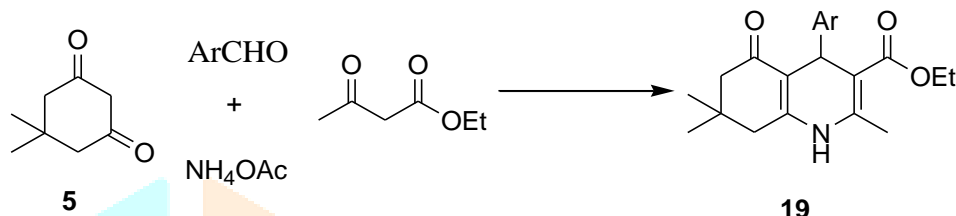


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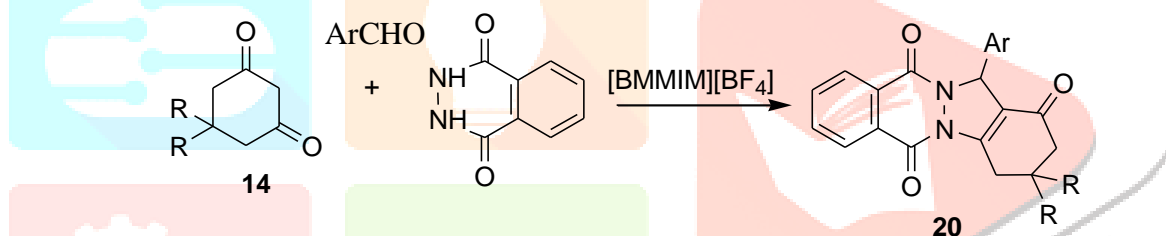
Gadekar, L. S. *et al.* have used one the diketo compound namely dimedone (**5**), for the synthesis of polyhydroquinolines (**19**) via four component reactions of aldehyde, ethyl acetoacetate and ammonium acetate in the presence of Scolecite catalyst in ethanol through Hantzsch reaction. This method provides remarkable advantages of shorter reaction time, excellent yields (**81-95%**), non-toxic.²³

**SCHEME 12**

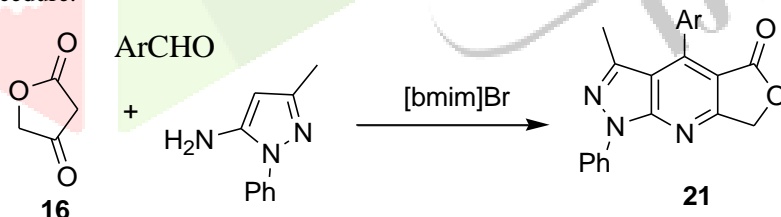
In this continuation using dicarbonyl group, an enantioselective route for the Hantzsch reaction using a chiral BINOL -phosphoric acid organocatalyst has been developed under relatively mild conditions with yields (**52-92%**) for a range of aromatic aldehydes. This method provides access to pharmaceutically dihydropyridines(**19**) and reagents for enantioselective hydrogenation reactions.²⁴

**SCHEME 13**

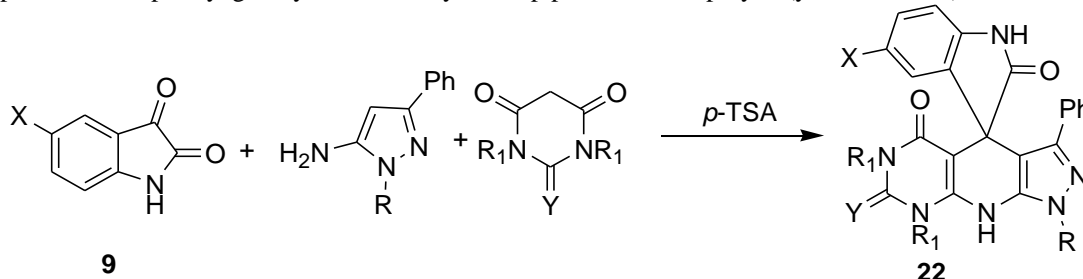
Fazaeli *et al* have established through dicarbonyl compounds that the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ($[\text{bmim}]\text{BF}_4$) offered the best results in terms of yield of the 2*H*-Indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives (**20**). It was observed that a homogeneous reaction medium proved beneficial for the yields (**82-92%**) of the reaction.²⁵

**SCHEME 14**

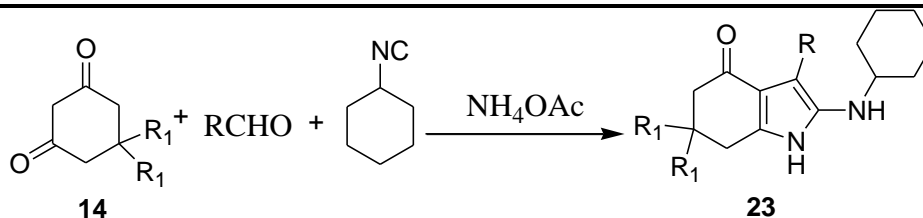
Adopting with dicarbonyl compounds, Da-Qing Shi *et al.* synthesized the compounds of furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-5(7*H*)-one derivatives (**21**) via the three-component reaction of an aldehyde, 5-aminopyrazole and tetronic acid (**16**) in ionic liquid without any catalyst. This method has the benefit of easier work-up, mild reaction conditions, high yields and an environmentally benign procedure.²⁶

**SCHEME 15**

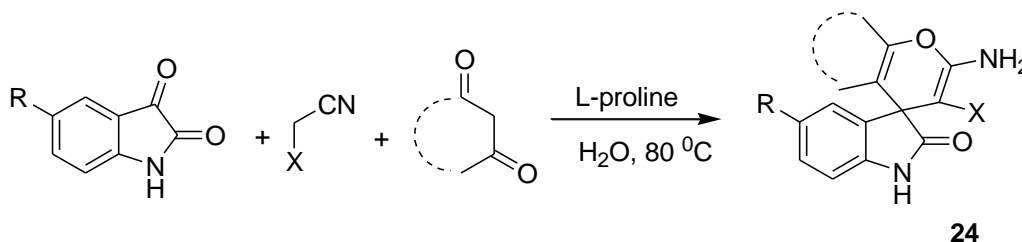
Employing through diketo group, An efficient method for the preparation of spiro[indoline-pyrazolo[4',3':5,6] pyrido[2,3-*d*]pyrimidine] derivatives (**22**) using readily available starting materials provide noticeable advantages of this new method which are novelty, operational simplicity, good yields and easy workup procedures employed (yields **78-98%**).²⁷

**SCHEME 16**

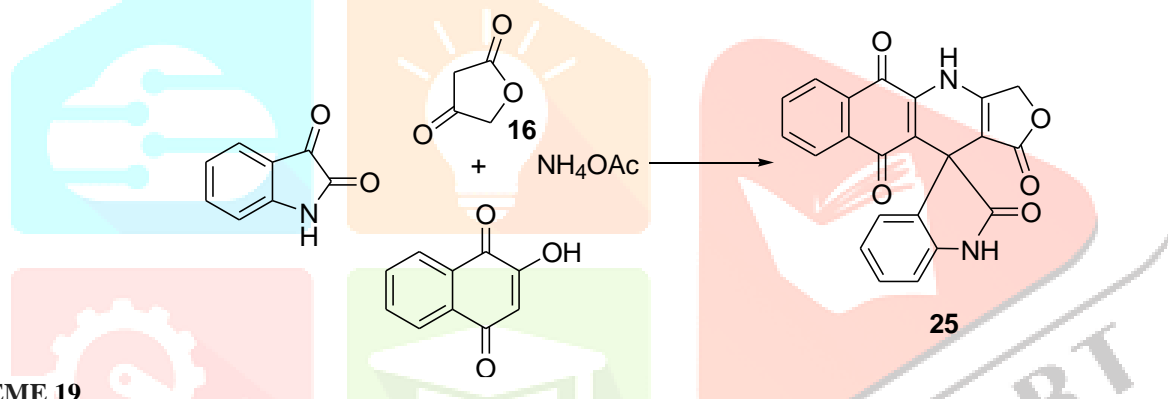
Work up procedure with cyclic diketo group (**14**), the new route of four components such as 1,3-diketo compounds (**14**), aromatic aldehyde, ammonium acetate and cyclohexyl isocyanide provides a simple route synthesis of 3-aryl-2-cyclo hexylamino-6,7-dihydro-1*H*-indole-4(5*H*)-ones (**23**) using ferric perchlorate as the catalyst. The reaction in the presence of $\text{Fe}(\text{ClO}_4)_3$ requires shorter reaction times than that used in the case of KHSO_4 , but gives higher yields (**87-94%**).²⁸

**SCHEME 17**

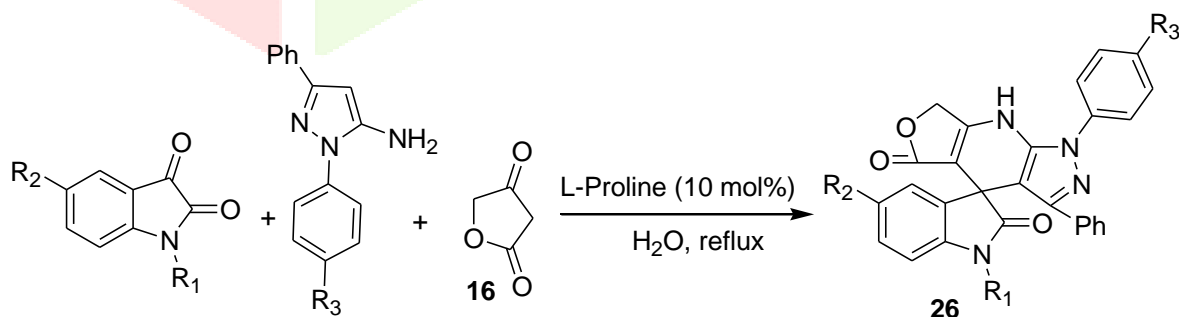
Li J and co-workers demonstrated the green synthesis of a library of spirooxindole derivatives (24) *via* a three-component reaction between isatins, nitriles and cyclic 1,3-dicarbonyl compounds employing L-proline (10mol%) as catalyst in water at 80 °C. A library of 28 compounds was synthesized from variously substituted isatins, malononitriles or cyanoacetic esters and (hetero)cyclic and acyclic 1,3-dicarbonyl compounds in excellent yields (76-95%)²⁹.

**SCHEME 18**

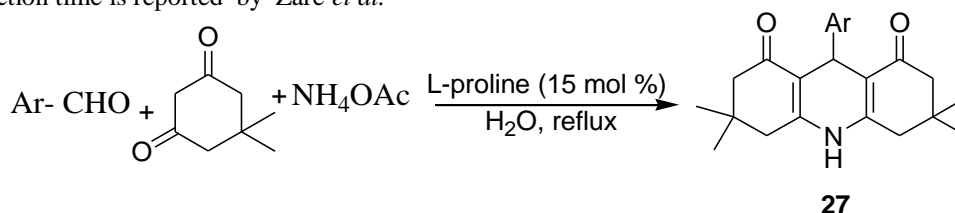
The main advantages of cyclic diketo compound are the significant decrease of reaction times and improvement of yields. This new procedure provides an efficient method for the synthesis of spiro[benzo[*g*]furo[3,4-*b*]quinoline-11,3'-indoline]tetraones (25) (73-90%). This method, based on four-component *p*-TSA catalyzed reaction under ultra-sonic irradiation, is very simple and convenient and would be applicable for the synthesis of different types of spiro[benzo furoquinoline-indoline]-tetraones.³⁰

**SCHEME 19**

An efficient synthesis of pyrazole fused spiro compounds (26) employing with diketo compounds (16) as summarized below was achieved *via* a three component reaction starting from isatins, tetronic acid and 1,3-diaryl-1*H*-pyrazole-5-amines. The reaction was carried out in the presence of 10mol% of L-proline in water under reflux conditions. The substrate scope was extended by the inclusion in the study of various isatins, acenaphthylene-1,2-dione and 2-hydroxynaphthalene-1,4-dione³¹

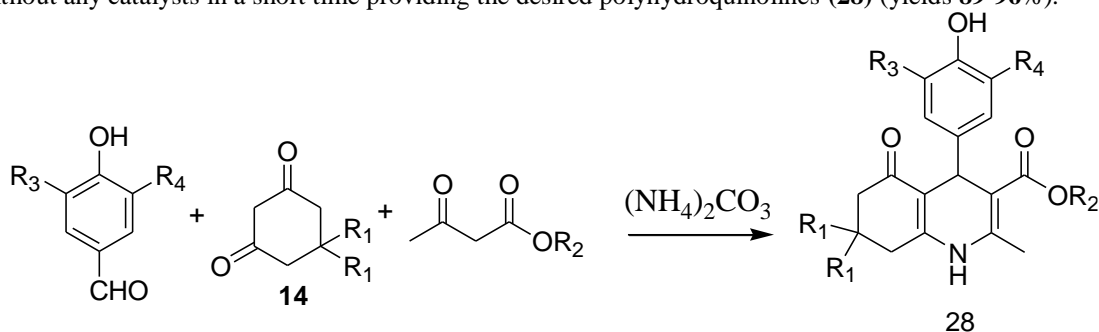
**SCHEME 20**

On the basis of cyclic diketo compounds, Multicomponent synthesis of mono and bis 4-substituted-1,4-dihydropyridines (27) from aldehydes, dimedone and ammonium acetate in the presence of an efficient recyclable catalyst, L-proline, in high yield (84-92%) and short reaction time is reported by Zare *et al.*³²



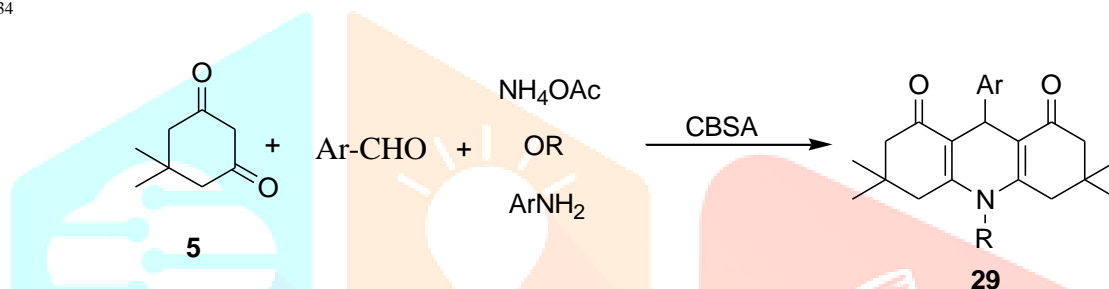
SCHEME 21

According to green chemistry concept, the reaction takes place using water as the solvent as well as ammonium carbonate as a solid ammonia source because it has low toxicity resulted in high yields. The key method of microwave irradiation can accelerate reaction rate, shorten reaction time, and improve product yields. Thus, the four-component reactions between the aromatic aldehydes, 1,3-cyclohexanediones (**14**), β -ketoesters and ammonium carbonate were conducted in water under microwave irradiation without any catalysts in a short time providing the desired polyhydroquinolines (**28**) (yields **89-96%**).³³



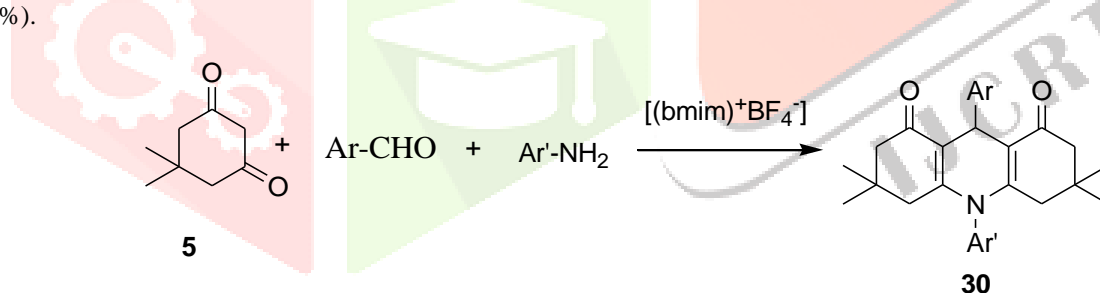
SCHEME 22

Proving with diketone compounds (**5**) to this section, carbon-based solid acid (CBSA) catalyst was discovered to be highly efficient, eco-friendly and recyclable heterogeneous catalyst for the multicomponent reaction of dimedone (**5**), aromatic aldehydes, and a nitrogen source (ammonium acetate or aromatic amines) under solvent-free conditions, giving rise to 1,8-dioxodecahydroacridines (**29**) in high yields. The present methodology offers several advantages, such as a simple procedure with an easy work-up, short reaction times, high yields and the absence of any volatile and hazardous organic solvents (yields **62-94%**).³⁴



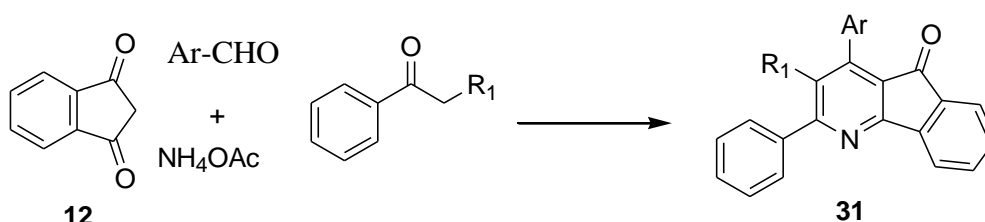
SCHEME 23

Rajanarendar *et al.*³⁵ have reported a multi-component one-pot synthesis of isoxazolyl polyhydroacridinediones (**30**) using an ionic liquid that provides a very efficient and convenient methodology over the existing methods. The wide scope of this three-component ionic liquid mediated reaction is that it tolerates the presence of electron withdrawing as well as electron releasing groups on benzene ring. Thus, this simple and green methodology may be a practical alternative to the existing procedures (yields **80-95%**).



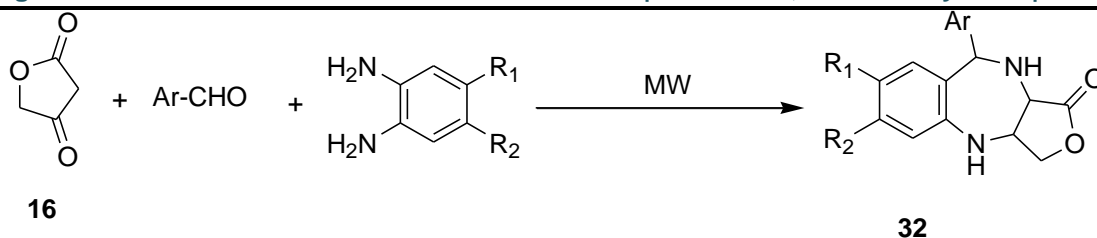
SCHEME 24

By the reason of cyclic diketone reactant, Tapaswi and co-authors demonstrated the synthesis of new indeno[1,2-*b*]pyridines (**31**) through an efficient catalyst ceric ammonium nitrate (CAN) in ethanol. Atom economy, excellent yields (**84-94%**) and mild reaction conditions are some of the important features of this protocol.³⁶

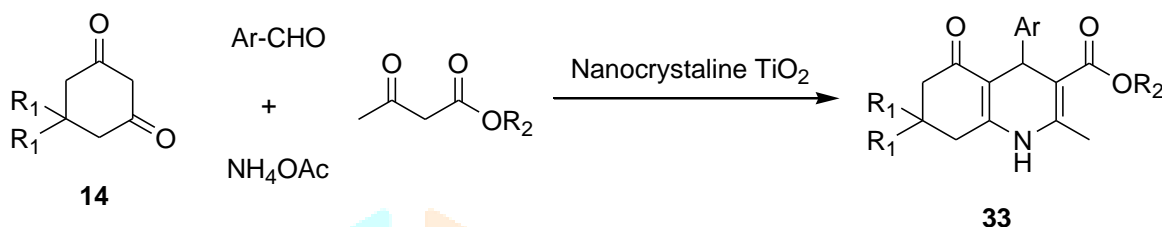


SCHEME 25

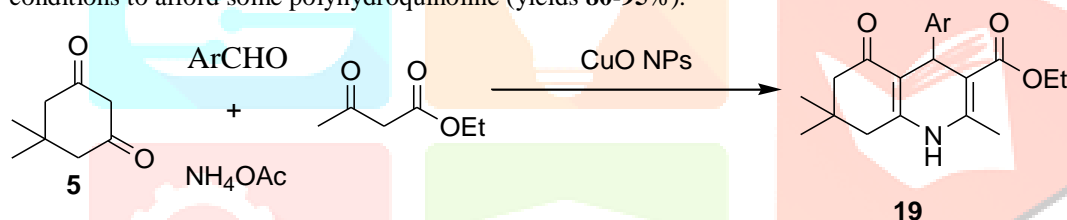
Wang *et al.*³⁷ have established a procedure using microwave irradiation to afford isoindole-fused furo[1,4]diazepine derivatives (**32**) that can serve as versatile building blocks for both organic and medicinal research. The reactions were conducted in aqueous solution under microwave irradiation using readily available and inexpensive starting diketone compound (**16**). This green synthesis has attractive characteristics such as the use of water as reaction media, concise conditions, short reaction periods, easy work-up and reduced waste production without the use of any strong acids or metal promoters (yields: **76-89%**).

**SCHEME 26**

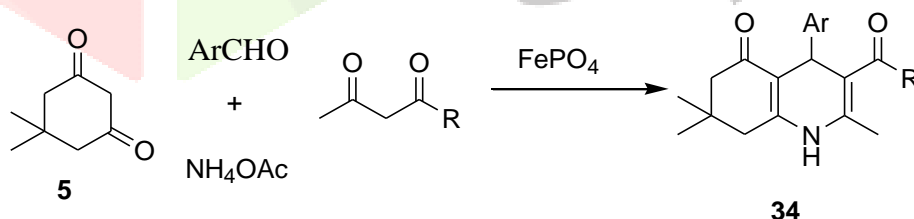
With the assistance of inexpensive starting diketo compound (**14**), The reaction of certain nanocrystalline TiO_2 as an efficient and reusable catalyst with the starting materials such as aldehydes, 1,3-dicarbonyl ketones (dimedone or 1,3-cyclohexanedione) (**14**), ethyl acetoacetate or methyl acetoacetate and ammonium acetate leads to the formation of polyhydroquinoline derivatives (**33**) via four-component coupling reactions under solvent free conditions. The reported method is mild, rapid and has the features such as heterogeneous catalysis, recyclability of the catalyst and purification of products without chromatographic methods (Yields **82-90%**).³⁸

**SCHEME 27**

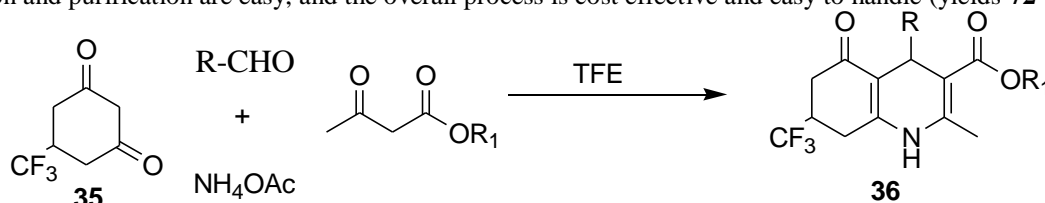
1,3-cyclic diketo group (**5**) have been focused for efficient method for the synthesis of a variety of polyhydroquinoline derivatives (**19**) via an improved Hantzsch reaction catalyzed by nano CuO . The reaction conditions are mild and the reaction gives excellent yields of the products. This method does not involve the use of toxic solvents thus it is an environmentally friendly process. The multi-component reactions dimedone (**5**), aldehyde ethyl acetoacetate and ammonium acetate were carried out under solvent-free conditions to afford some polyhydroquinoline (yields **80-95%**).³⁹

**SCHEME 28**

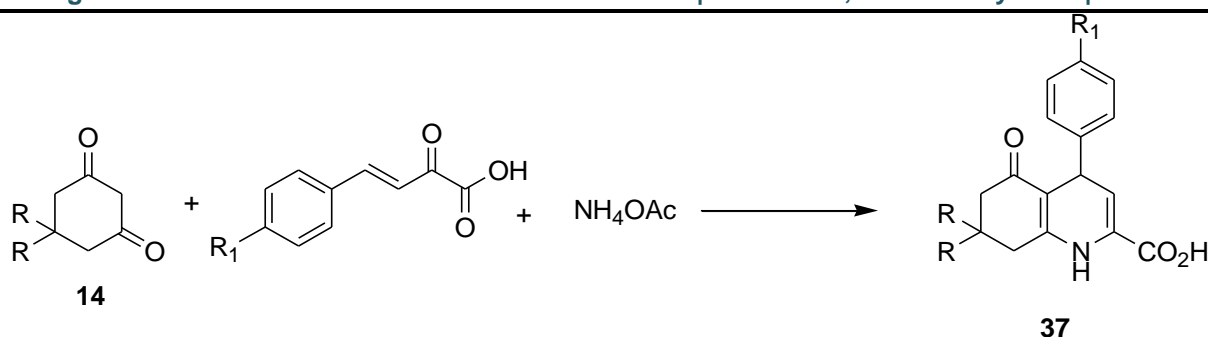
Behbahani *et al*⁴⁰ have utilized diketo compounds to offer the key stages of green method due to be used with heterogeneous and reusable catalyst accompanied by utilizing ethanol as a solvent and environmentally friendly, and convenient synthetic method for the synthesis of biologically important polyhydroquinoline derivatives (**34**) via an improved Hantzsch reaction catalyzed by FePO_4 . The reaction which does not involve the use of volatile organic solvents, are mild condition gives products in excellent yields (**84-96%**).

**SCHEME 29**

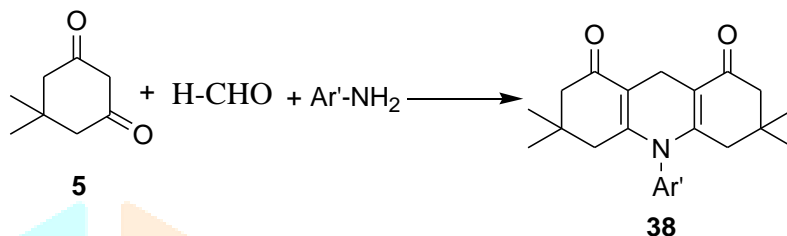
Trifluoromethylated diketo compounds have been involved for efficient synthesis of some new hexahydroquinoline derivatives (**36**) was reported via four-component coupling reactions of aldehydes, 1,3-dicarbonyl ketones (5-trifluoromethyl-1,3-cyclohexanedione) (**35**), ethyl acetoacetate or methyl acetoacetate and ammonium acetate in the solvent media of trifluoroethanol. Product isolation and purification are easy, and the overall process is cost effective and easy to handle (yields **72-98%**).⁴¹

**SCHEME 30**

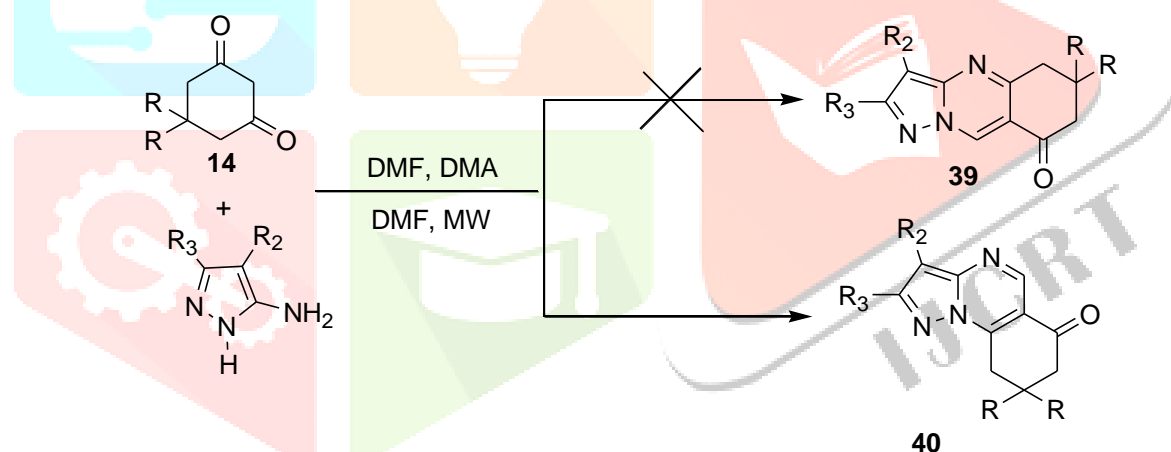
A simple and fast three-component reaction has been established for the synthesis of new and biologically active hexahydro-2-quinolinecarboxylic acid (**37**). The reaction was performed using cyclocondensation reaction of arylmethylidenepyruvic acids, 1,3-cyclohexandiones (**14**) and ammonium acetate under solvent-free conditions at room temperature. The present new synthesis shows attractive green chemistry characteristics, such as easy work-up, high yields (92-98%), short reaction time and environmentally friendly character.⁴²

**SCHEME 31**

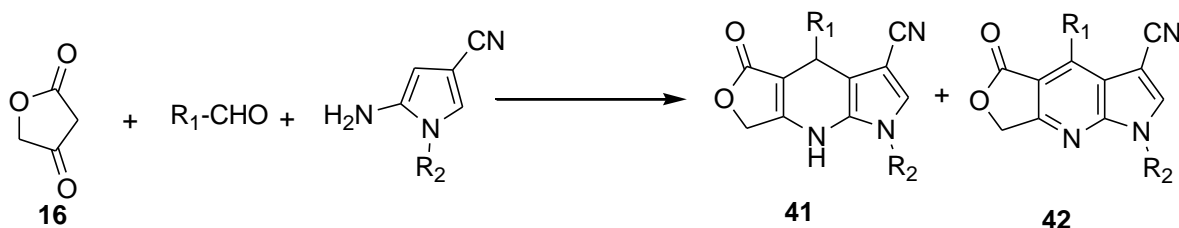
The methods for the construction of acridinediones (38) *via* the one-pot Hantzsch condensation of an aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione, and aniline or 4-methylaniline in refluxing water have been established by Xia et al. This present methodology has then been extended to the four-component reaction for the synthesis of polyhydroquinoline derivatives which possess an environmentally friendly and efficient procedure providing good to excellent yields (69-86%).⁴³

**SCHEME 32**

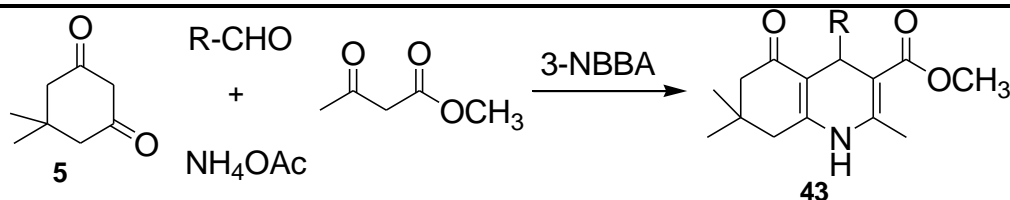
Microwave-assisted three-component reaction has been established for the synthesis of 8,9-dihydropyrazolo[1,5-*a*]quinazolin-6(7*H*)-ones starting from 5-aminopyrazole derivatives, cyclic 1,3-dicarbonyl compounds (14) and dimethylformamide dimethylacetal (DMFDMA) in DMF. This method afforded regioselectively 8,9-dihydropyrazolo[1,5-*a*]quinazolin-6(7*H*)-ones (40) rather than the corresponding dihydropyrazolo[5,1-*b*]quinazolin-8(5*H*)-ones (39) (yields 82-89%).⁴⁴

**SCHEME 33**

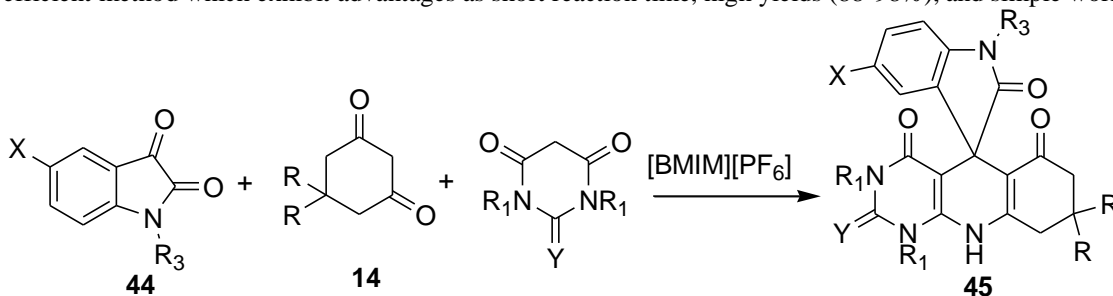
An efficient and practical route to 7-azaindole framework has been developed by one-pot, three-component cyclocondensation of *N*-substituted 2-amino-4-cyanopyrroles, various aldehydes, and active methylene compounds in ethanol. Reactions involving tetrone acid gave carbocyclic fused 7-azaindoles. This strategy is very useful in diversity-oriented synthesis (DOS). It should be noted that under these reaction conditions, the major products are the fused dihydropyridines (41) (yields 35-80%), and only in the case of 5-methylfurfural and octanal the final products were carbocyclic fused 7-azaindoles (42) (yields 24, 94%).⁴⁵

**SCHEME 34**

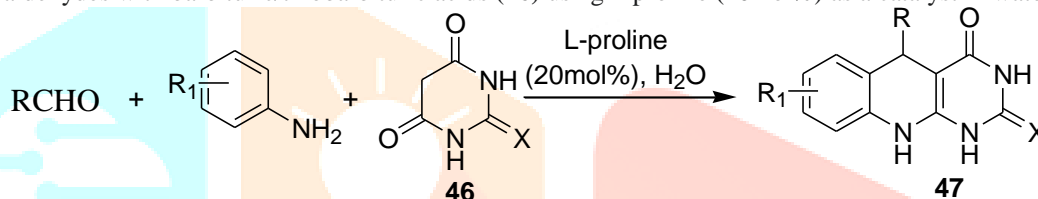
An efficient synthesis of polyhydroquinolines (43) is achieved *via* a four-component reaction of aldehydes, dimedone (5), active methylene compounds, and ammonium acetate in one-pot under solvent-free conditions using 3-nitrophenylboronic acid as a catalyst. The key advantages are the short reaction time, high yields, simple workup and purification of products (yields 87-95%).⁴⁶

**SCHEME 35**

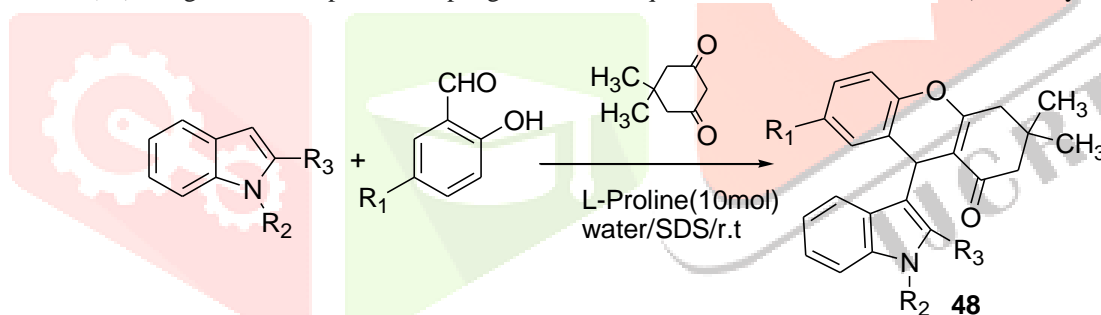
An efficient and environmentally friendly multi-component synthesis of substituted spiro[chromeno[2,3-*d*]pyrimidine-5,3'-indoline]tetraones (**45**) with alum as a catalyst and [Bmim]PF₆ as media is described. The combination of isatin (**44**), barbituric acid, and cyclohexane-1,3-dione derivatives (**14**) in the presence of alum as a catalyst and [Bmim]PF₆ as media was found to be a suitable and efficient method which exhibit advantages as short reaction time, high yields (88-98%), and simple workup.⁴⁷

**SCHEME 36**

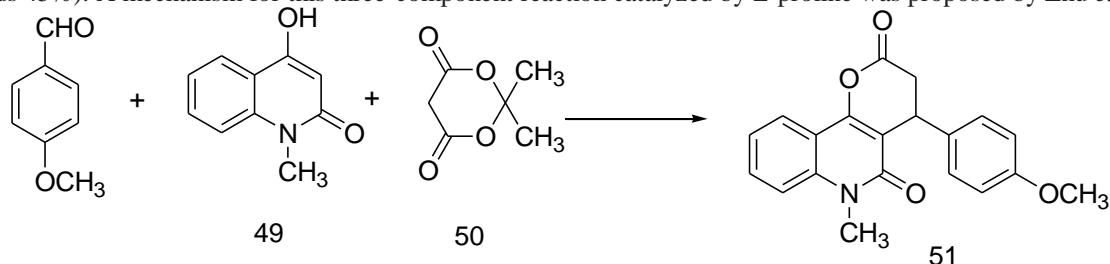
A three component synthesis of 5-arylpyrimido[4,5-*b*]quinolinediones (**47**) (yield 82-92%) was evolved by the reaction of arylamines, aryl aldehydes with barbituric/thiobarbituric acids (**46**) using L-proline (20mol%) as a catalyst in water⁴⁸

**SCHEME 37**

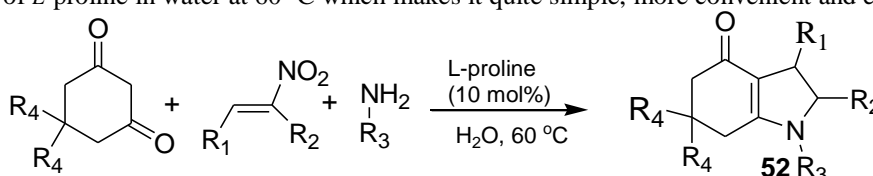
With the assistance of inexpensive starting diketo compound (**14**), Ganguly and co-workers achieved the synthesis of compounds (**48**) using a three component coupling under mild aqueous micellar conditions in (86-96% yields).⁴⁹

**SCHEME 38**

The compounds aryl-6-methyl-3,4-dihydro-2*H*-pyrano[3,2-*c*]quinolin-2,5(6*H*)-diones (**51**) were synthesized via the three-component reactions of aromatic aldehydes, 4-hydroxy-1-methylquinolin-2(1*H*)-one(**49**), and Meldrum's acid(**50**) catalyzed by L-proline (yields 45%). A mechanism for this three-component reaction catalyzed by L-proline was proposed by Zhu *et al*⁵⁰.

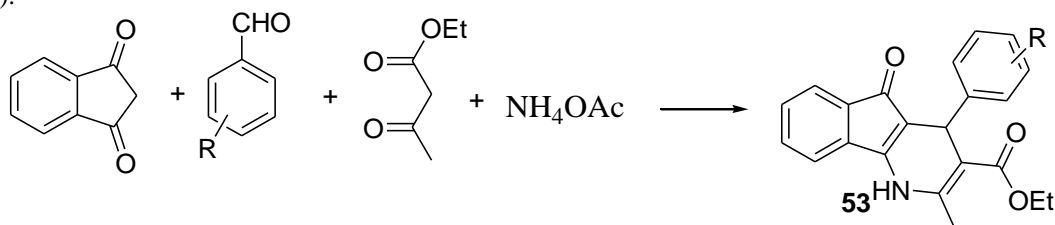
**SCHEME 39**

Zhang *et.al*⁵¹ have established an efficient domino approach for the synthesis of tetrahydro-4*H*-indol-4-one derivatives (**52**). The use of catalytic amount of L-proline in water at 60 °C which makes it quite simple, more convenient and environmentally benign.

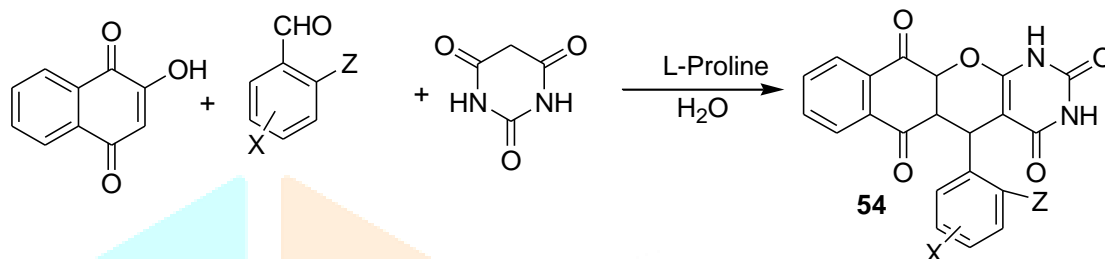


SCHEME 40

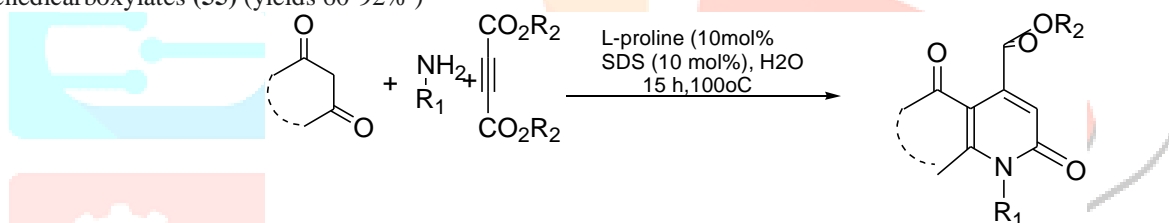
A synthetic transformation starting from ethyl acetoacetate, 1,3-indanedione and ammonium acetate was also reported for the synthesis of unsymmetrical fused 1,4-DHPs (**53**) in the presence of *L*-proline in water under reflux conditions by Behbahani *et al* (yields 86-98%).⁵²

**SCHEME 41**

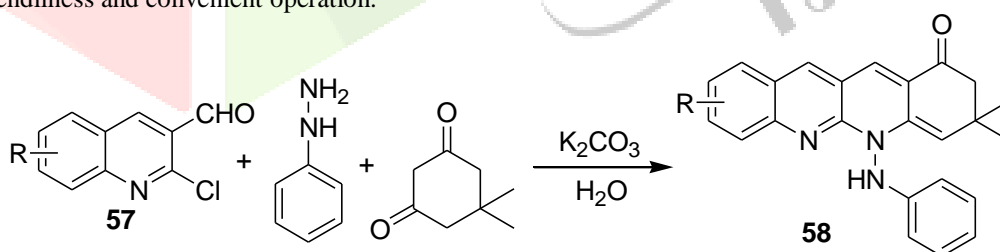
Mofakham, H., *et al*⁵³ have developed a green and efficient organo catalyzed multi component reaction for the synthesis of pyrimidine-containing chromene derivatives(**54**) via a domino Knoevenagel/Michael/cyclization sequence from 2-hydroxy-1, 4-naphthoquinone with barbituric acid in the presence of a catalytic amount of *L*-proline in water in moderate to good yields(65-80%).

**SCHEME 42**

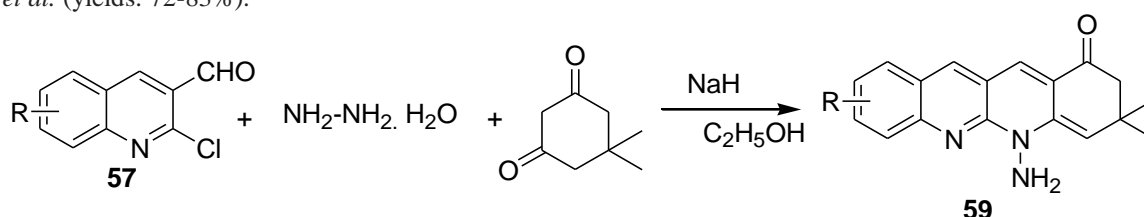
Sarkar and Mukhopadhyay have developed a simple three component procedure for the synthesis of fused *N*-substituted 2-pyridone derivatives (**56**) under *L*-proline catalysis in water starting from cyclic 1,3-diketones, primary amines, and dialkyl acetylenedicarboxylates (**55**) (yields 60-92%)⁵⁴

**SCHEME 43**

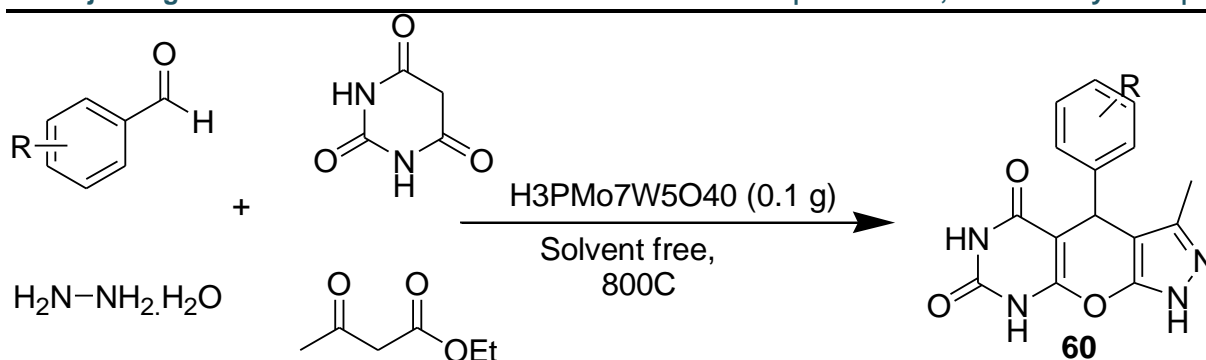
Rajendran *et al*⁵⁵. have described a facile and significant one pot procedure for the preparation of functionalized dibenzo[b,g][1,8]naphthyridine derivatives (**58**) by three-component reaction of 2-chloroquinoline-3-carbaldehyde(**57**), 1,3-dicarbonyl compound and phenyl hydrazine catalyzed by potassium carbonate in aqueous media (yields 56-72%) This new protocol is one of highly expedient methods for the synthesis of naphthyridine compounds and has the advantages of environmental friendliness and convenient operation.

**SCHEME 44**

Recently, A one-pot, three-component synthesis of 5-amino-3,3-dimethyl-3,5-dihydro-2H-dibenzo[b, g][1,8] naphthyridin-1-ones (**59**) starting from 2-chloro-3-formyl quinolines (**57**) and Dimedone using base catalyst in ethanol has been accomplished by Rajendran *et al*. (yields: 72-83%).⁵⁶

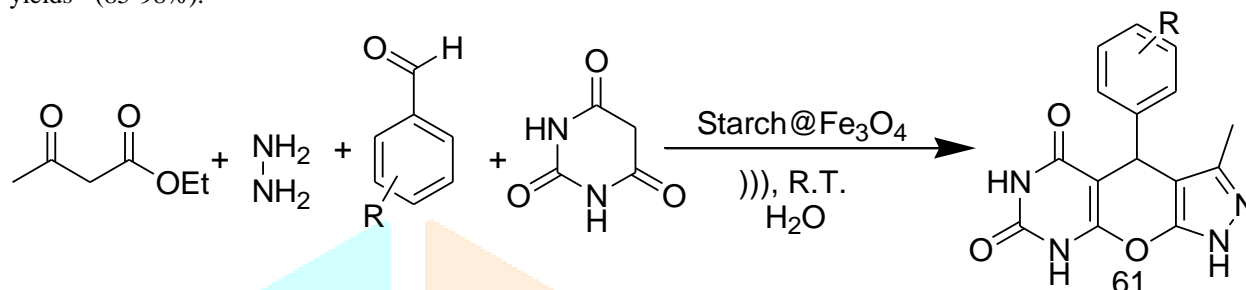
**SCHEME 45**

Under the solvent free condition, substituted benzaldehyde, hydrazine hydrate, barbituric acid, and ethyl acetoacetate are used as a reactant with the presence of $H_3PMo_7W_5O_{40}$. This multicomponent synthesis yields a compound(**60**) as pyrazolopyranopyrimidines derivatives⁵⁷ (85-96%).



SCHEME 46

Starting precursors namely ethyl acetoacetate, hydrazine hydrate, aromatic aldehydes, barbituric acid are used in the presence of starch with iron oxide in water medium to lead the formation of pyrazolopyranopyrimidine derivatives(61) with magnificent yields⁵⁸ (85-98%).



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