Versatile Precursors in Organic Synthesis

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By

Okram Mukherjee Singh
and Thokchom Prasanta Singh

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CHAPTER 1

1,3-DIKETONES

1. Introduction

The importance of 1,3-diketones (*β*-diketones) **1** (Figure 1) is difficult to assess in synthetic organic chemistry, but it is one of the most valuable and fundamental intermediates due to the presence of two carbonyl groups in it. Their chemistry is closely associated with well-known name reactions in organic chemistry such as Claisen, Knoevenagel, Michael, etc. The high reactivity of 1,3-diketones helps in broad prospects for constructing C-C bonds, carbo- and heterocycles (Shokova et al., 2015). They are also an excellent versatile intermediate in multicomponent reactions, particularly regio- and stereoselective, which is especially important in synthesizing potentially, biologically active compounds (Bonne et al., 2010; and Colombo and Peretto, 2008). They also act as bidentate ligands in metal catalysis as well as luminescent materials (Vigato et al., 2009).

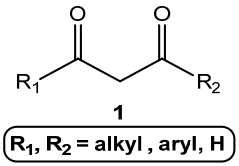
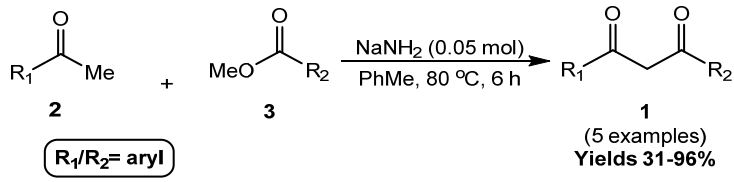


Figure 1. A simple structure of 1,3-diketone compound.

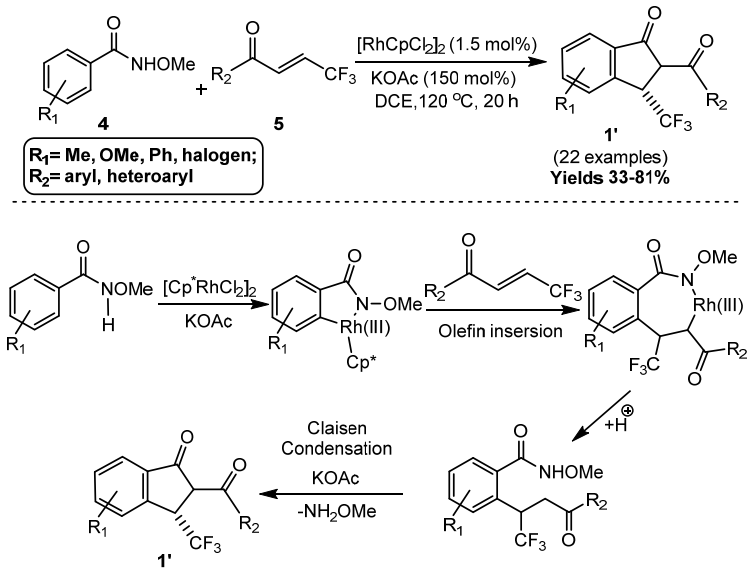
2. Synthesis of 1,3-Diketones

One of the significant methods for the synthesis of *β*-diketones is based on Claisen condensation, which has been known since 1887. It involves acylation of monocarbonyl compounds in the presence of catalysts favoring their enolization (Kel'in, 2003; Kel'in et al., 2003). Acetophenone derivatives **2** were converted into *β*-diketones *via* acylation with aromatic esters **3** under the classical Claisen conditions using $NaNH_2$ as a catalyst, as reported by Wang et al. (2012), (Scheme 1).



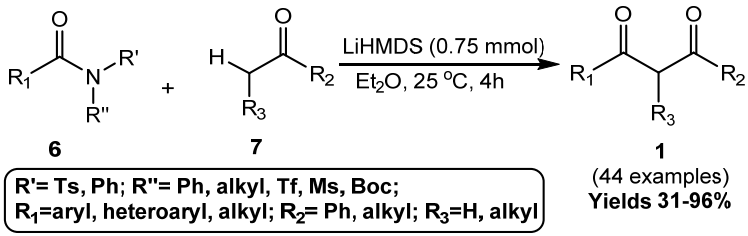
Scheme 1. Synthesis of 1,3-diketones by Claisen Condensation.

The synthesis of 2-acyl-3-trifluromethylindanones **1'** by coupling with *N*-methoxybenzamides **4** and *β*-trifluoromethyl-*α,β*-unsaturated ketone **5** using $[RhCp^*Cl_2]_2$ in the presence of KOAc, DCE at 120 °C was demonstrated by Chaudhary et al. (2020). The reaction mechanism involved sp^2 C-H activation, followed by Claisen condensation involving C-N bond cleavage to form the products (Scheme 2).



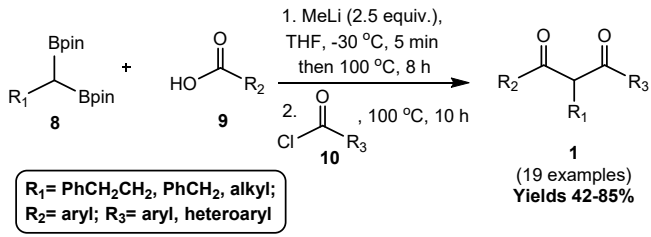
Scheme 2. Synthesis of 1,3-diketone using 2-acyl-3-trifluoromethylindanones.

Chen et al. (2020) reported the synthesis of 1,3-diketones using different tertiary amides **6** with ketones **7** in the presence of lithium bis(trimethylsilyl)amide (LiHMDS). The methodology gave the corresponding 1,3-diketones in good to excellent yields *via* C-N cleavage of amides and deprotonation of ketones. The reactions were performed at room temperature without any catalyst. The advantages of this method are its broad scope, good functional group tolerance of substrates and the potential of this protocol in organic synthesis and industrial manufacture (Scheme 3).



Scheme 3. Synthesis of 1,3-diketones using 3° amides with ketone.

Then, the synthesis of asymmetric 1,3-diketones through diacylation of 1,1-diborylalkanes **8** using two different acyl groups i.e., **9** and **10** were explored (Zou et al., 2019). In this method, an enolate boron species was firstly formed by introducing an acyl group and then it reacted again with another acyl group to form 1,3–diketone (Scheme 4).

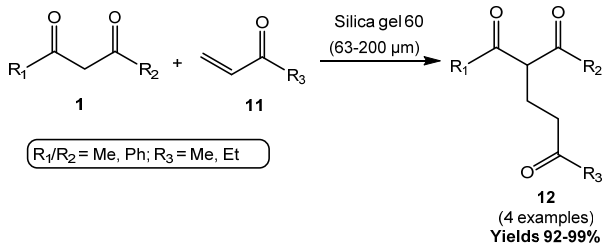


Scheme 4. General synthesis of 1,3-diketones.

3. Functionalization of 1,3-Diketones

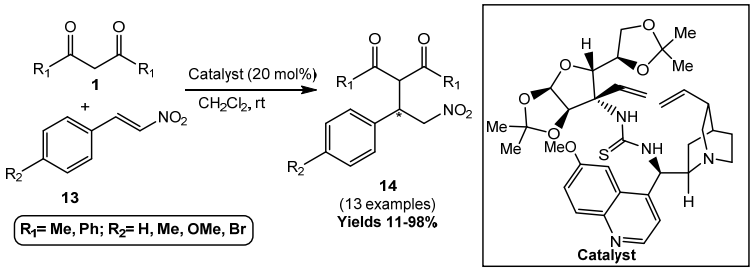
The functionalized 1,3-diketones are clinically significant molecules due to their exhibition of various biological properties such as antibacterial,

antiviral, insecticidal, etc. (Sheikh et al., 2013). The metal-catalyzed C-H and C-O functionalization reactions are also significant because of their potential to streamline organic synthesis by avoiding the prior preparation of activated substrates and reducing the quantity of waste by-products, and thereby making more atom-economic of the reactions (Dooley et al., 2013). In this context, the Michael addition is widely famous as well as recognized as an efficient and vital reaction for the formation of C-C bonds in organic synthesis (Axelsson et al., 2020). The report on a silica gel-mediated catalyst-free and solvent-free Michael addition of 1,3-dicarbonyl compound in the presence of methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) **11**, giving rise to corresponding adducts **12** without volatilization in good yields, was reported in 2020 by Tanemura and Rohand (2020), (Scheme 5).



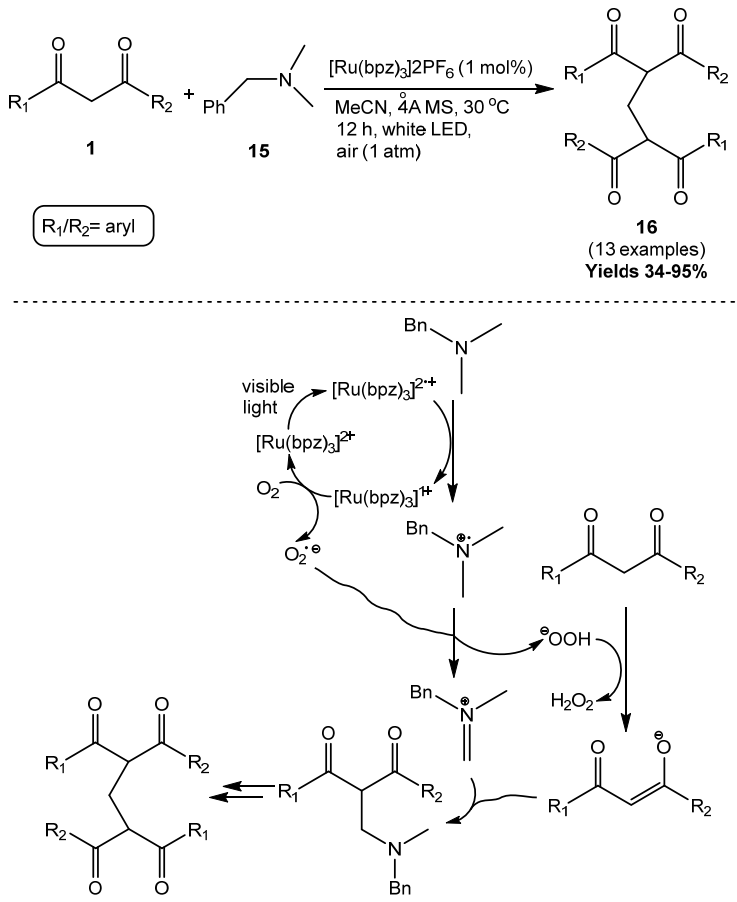
Scheme 5. *α*-Position functionalization of 1,3-diketone using vinyl ketones.

The Michael addition of 1,3-dicarbonyl compounds to nitrostyrenes **13** to afford the corresponding adducts **14** in excellent yields (up to 98%) was elaborated on (Scheme 6). This protocol used a bifunctional organocatalyst bearing a cinchona-based alkaloid unit, as reported by Roncak et al. (2020).



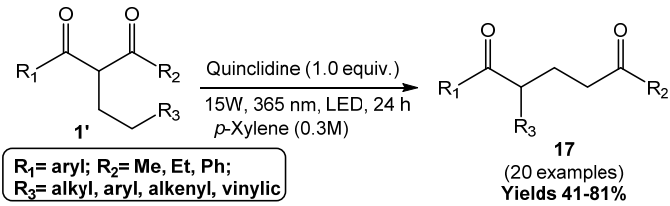
Scheme 6. Asymmetric Michael addition of 1,3-dicarbonyl to *trans*-nitro olefins.

Yoo et al. (2012) developed an efficient protocol for synthesizing methylene-bridged 1,3-diketones **16** through an aerobic photocatalytic oxidative coupling reaction between 1,3-diketones and *N,N*-dimethylbenzyl amine **15**. The mechanism starts with the initial excitation of $[Ru(bpz)_3](PF_6)_2$ by visible light and the subsequent reductive quenching by *N,N*-dimethyl benzylamine generating amine radical cation along with a strongly reducing $[Ru^{I}(bpz)_3]$ complex. The oxygen gas regenerates the photocatalyst and the resulting oxygen radical anion abstracts the proton of the radical cation to furnish another reactive iminium intermediate. This transient species was intercepted by deprotonated nucleophiles derived from 1,3-diketones **1** to give the coupling products **16** (Scheme 7).



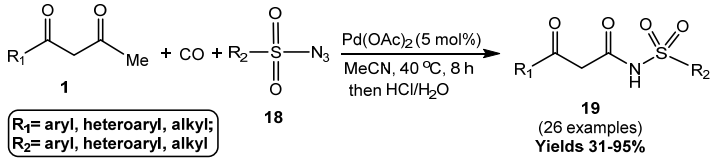
Scheme 7. Photocatalysis of *N,N*-dimethylbenzylamine and 1,3-diketones.

The photolytic [1,3]-benzoyl migration of *β*-benzoyl carbonyl compounds **1'** promoted by organic amine was reported by Zhang et al. (2020). This migration follows a Norrish-Yang cyclization and a retro-Aldol reaction under black light (365 nm) or visible light irradiation. 1,3-diketones bearing two different alkyl (R_2–alkyl) groups that could tolerate giving the benzoyl-shifted products **17** in moderate to good yield (Scheme 8).



Scheme 8. Photolytic formation of 1,5-diketones from 1,3-diketones.

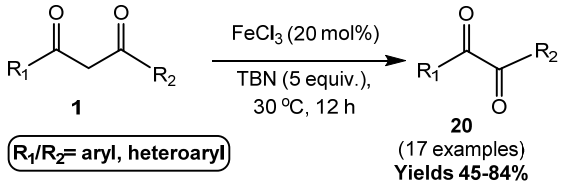
The amidation of 1,3-diketones has been developed (Gu et al., 2020) using carbon monoxide and organic azides **18** in the presence of a Pd-catalyst. This process produces a variety of *β*-ketoamides **19** under mild ligand-, oxidant- and base-free conditions (Scheme 9).



Scheme 9. Synthesis of *β*-ketoamide from 1,3-diketones.

The synthesis of 1,2-diketones **20** through the selective C-C bond cleavage of 1,3-diketones under mild reaction conditions in air by using $FeCl_3$ as the catalyst and tert-butyl nitrite (TBN) as the oxidant, without any solvent, was reported by Huang et al. (2011). This reaction of unsymmetrical 1,3-diketones was highly selective, which could tolerate both electron-donating and electron-withdrawing substituents in the aryl ring of 1,3-diketones to give the corresponding 1,2-diketones **20** in good yields (Scheme 10). Further, the steric hindrance on the aryl ring played a minor role in the reaction. For example, 1- and 2-naphthyl-substituted 1,3-

diketones transformed smoothly to afford the corresponding 1,2-diketones in good yields.

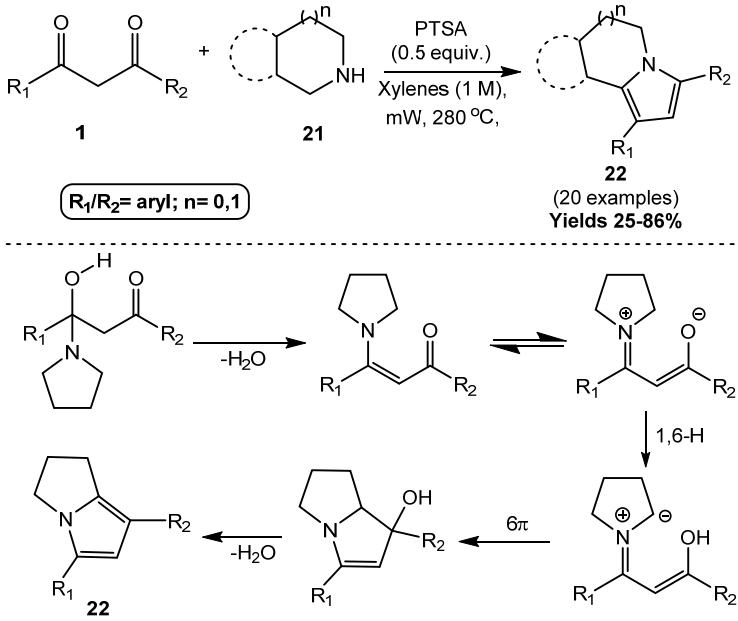


Scheme 10. Synthesis of 1,2-diketones from 1,3-diketones.

4. Application of 1,3-Diketones

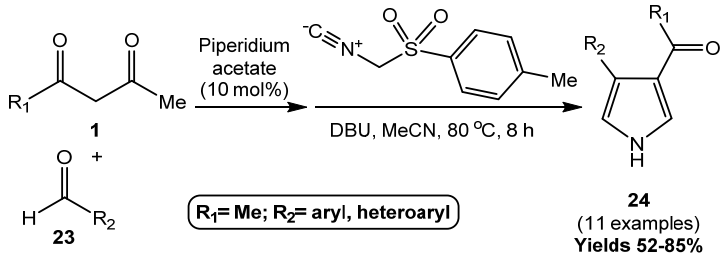
4.1 Synthesis of *N*-containing heterocycles

The 1,3-diketones and cyclic amines **21** readily react under microwave irradiation in the presence of *para*-toluene sulphonic acid (PTSA) to form ring-fused pyrroles in a single operation (Deb and Seidel, 2010). The mechanism involved the formation of *N,O*-acetal, which was simultaneously dehydrated to enaminone. This enaminone undergoes a sequential reaction involving a 1,6-H-shift and 6π-electrocyclization to yield an alcohol bearing intermediate. Finally, the subsequent water loss gives rise to pyrrole **22** (Scheme 11).



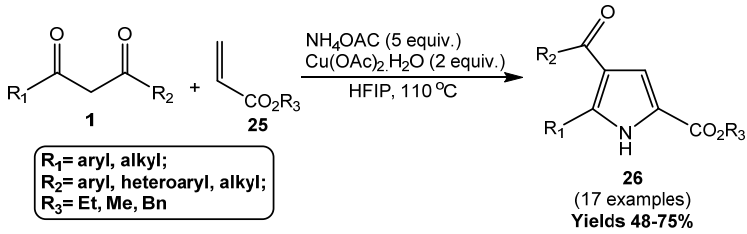
Scheme 11. Formation of ring-fused pyrroles from 1,3-diketones.

The protocol for efficient synthesis of 3,4-disubstituted pyrroles **24** utilizing the three-component reaction of aldehydes **23**, 1,3-diketones and toluene sulfonyl methyl isocyanide (TosMIC) in one-pot conditions was reported by Manasa et al. (2018). This reaction involves a Knoevenagel condensation between an aldehyde and a diketone substrate to give an unsaturated alkene intermediate, which further undergoes a Michael addition with TosMIC in the presence of the 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) leading to 3,4-disubstituted pyrroles (Scheme 12).



Scheme 12. Synthesis of disubstituted pyrroles from 1,3-diketones.

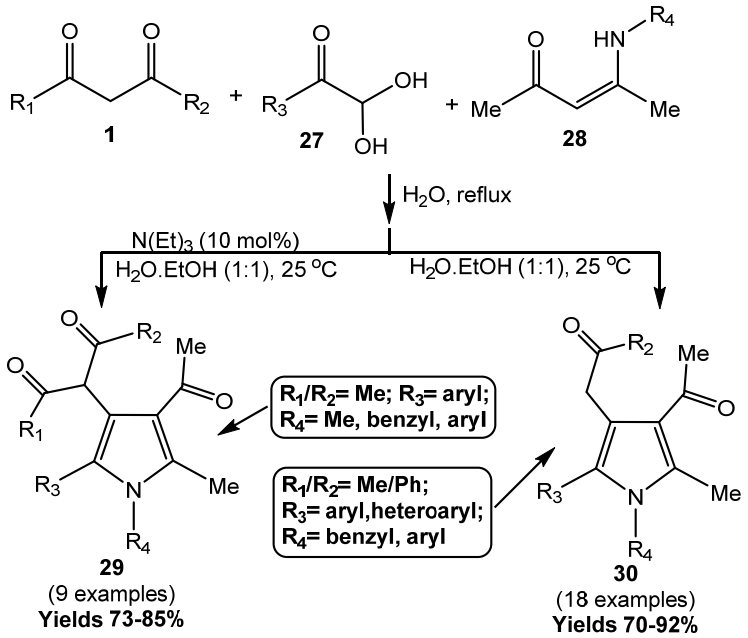
The synthesis of trisubstituted pyrroles **26** from 1,3-diketones was demonstrated by He et al. (2020). They used a copper-mediated one-pot synthesis from 1, 3-diketones and acrylates **25** using ammonium acetate as the nitrogen source and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the solvent (Scheme 13). The reaction achieves C-C and C-N bond formations and provides an efficient approach to access highly functionalized pyrroles without further raw material preparation.



Scheme 13. Synthesis of trisubstituted pyrroles from 1,3-diketones.

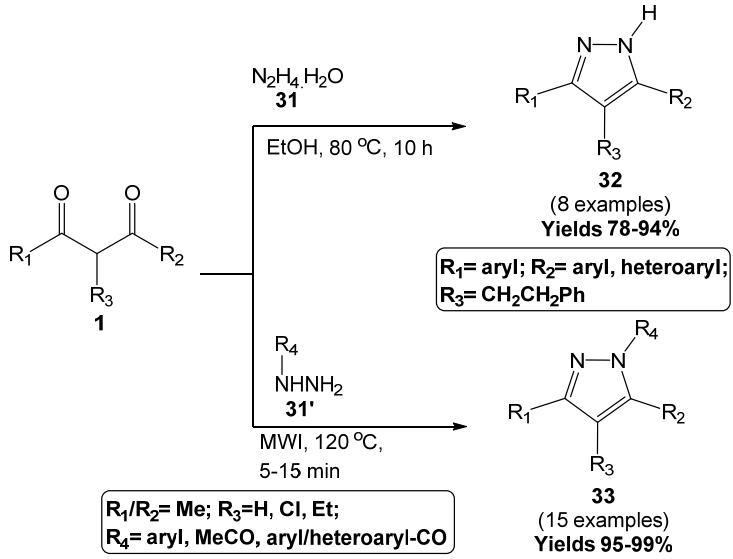
Then, the methodology for synthesizing polyfunctionalized pyrroles **29-30** *via* tetraone derivatives by a three-component reaction between arylglyoxals **27**, 1,3-diketones and enaminoketones **28** was elaborated on by Anary-Abbasinejada et al. (2020). Two types of products were obtained, depending upon the reaction conditions employed. The method's

advantages were the easy workup and using water or an ethanol-water mixture as the environmentally green solvent (Scheme 14).



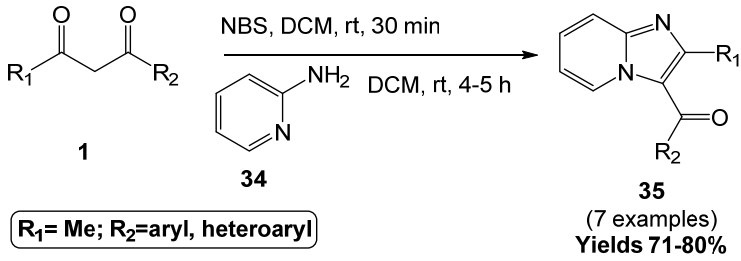
Scheme 14. Synthesis of polyfunctionalized pyrroles from 1,3-diketones.

A series of *α*-substituted 1,3-diketones were reacted with hydrazine hydrate **31** to produce trisubstituted pyrazoles **32** in excellent yields (Zou et al., 2019). However, a greener procedure for preparing pyrazoles **33** was developed from 1,3-diketones and hydrazines/hydrazides **31'** (Vaddula et al., 2013). The eco-friendly method was accelerated by microwave heating under catalyst- and solvent-free conditions in 5-15 mins, as compared to traditional heating (Scheme 15).



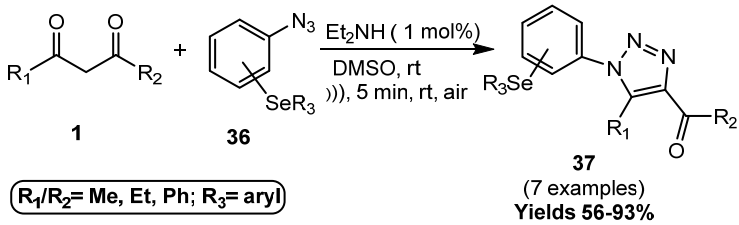
Scheme 15. 1,3-Diketones with hydroxylamines/hydrazines undergo condensation to give pyrazoles.

The simple protocol toward the regioselective synthesis of 1-aryl/heteroaryl-1-(2-methylimidazo [1,2-*α*]pyridin-3-yl)methanones **35** was developed (Aggarwal et al., 2016) by one-pot condensation of 2-aminopyridine **34** with 1,3-diketones. The reaction involves the intermediacy of 2-bromo-1,3-diketones formed *in situ* from 1,3-diketones using *N*-bromosuccinimide (NBS) in dichloromethane (DCM) by stirring at room temperature (Scheme 16).



Scheme 16. Synthesis of imidazo[1,2-*α*]pyridines from 1,3-diketones.

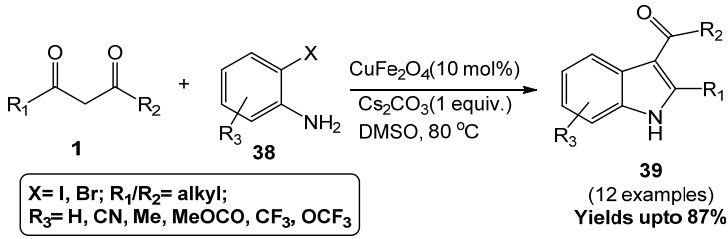
Costa et al. (2017) developed the organocatalytic enamine–azide [3+2] cycloaddition between 1,3-diketones and arylazidophenyl selenides **36** providing an efficient access to new ((arylselanyl)phenyl-1*H*-1,2,3-triazol-4-yl)ketones **37** in the presence of diethylamine (Et_2NH) and dimethyl sulfoxide (DMSO) as solvents. The sonochemically promoted reactions were found to be amenable to a range of 1,3-diketones or aryl azidophenyl selenides giving the desired products in good to excellent yields within short reaction times (Scheme 17).



Scheme 17. Synthesis of triazoles from 1,3-diketones.

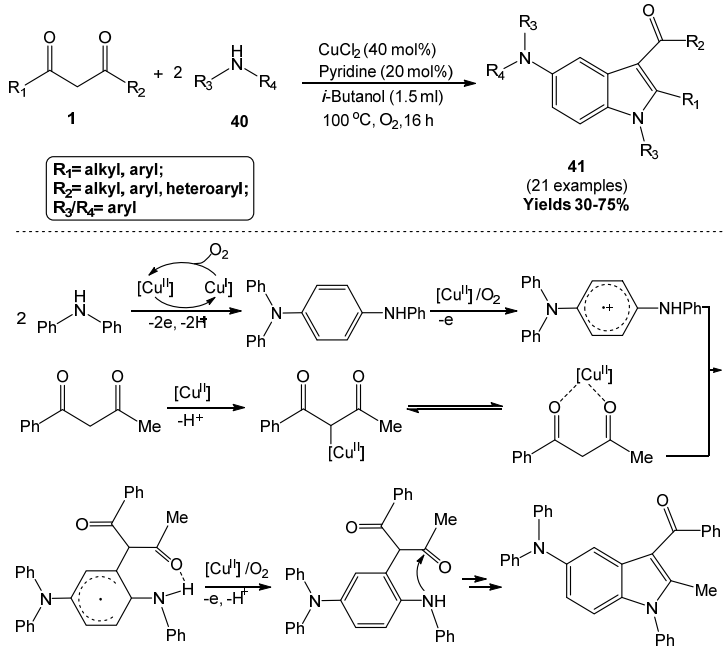
The synthesis of indole derivatives **39** from 1,3-diketones was successfully demonstrated by Vu et al. (2020). Here, 1,3-diketones were coupled with 2-halo substituted anilines **38** in the presence of the heterogeneous catalyst $CuFe_2O_4$ and the base Cs_2CO_3. The solvent used was DMSO and reacted

at 80 °C under argon for 16 h giving good yields of the products (Scheme 18).



Scheme 18. Annulation of 2-haloaniline with 1,3-diketones to give indoles.

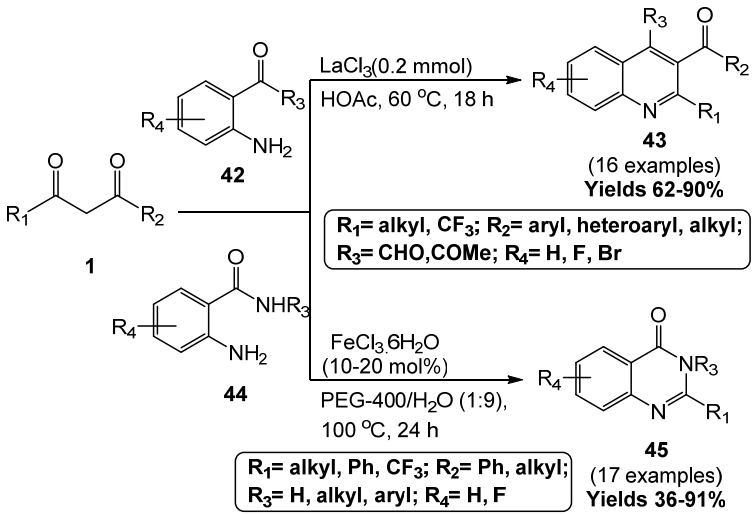
The direct synthesis of functionalized indoles **41** *via* single-electron oxidation (SEO) induced coupling of diarylamines **40** with 1,3-diketones was reported by Liang et al. (2019). It proceeds with good functional group and substrate compatibility, using a readily available and naturally abundant catalyst system, which affords a new class of indoles with the potential for discovery. $CuCl_2$ and pyridine initiated the coupling to afford the desired products **41** in moderate to good isolated yields in iso-butanol as the solvent. Moreover, 1,3-diketones containing an electron-donating group on the aryl ring yielded a much higher product than those with an electron-withdrawing group. The proposed mechanism involved the aerobic copper-catalyzed SEO of the substrate to give the functionalized indoles (Scheme 19).



Scheme 19. Functionalization of indoles *via a* single electron transfer mechanism.

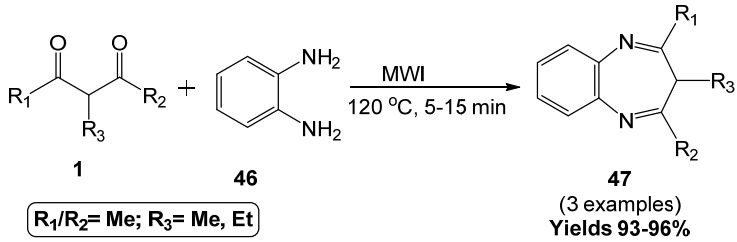
The regioselective and efficient synthesis of substituted quinolines **43** using the lanthanum chloride ($LaCl_3$) mediated Friedländer reaction was demonstrated by Chen et al. (2012). The reaction between an unsymmetrical 1,3-diketone with the corresponding 2-carbonyl aniline **42** gives high regioselective quinoline in moderate to excellent yields. However, the synthesis of 2-substituted quinazolinones **45** from the tandem reaction of 2-aminobenzamides **44** with 1,3-diketones *via* condensation, intramolecular nucleophilic addition, C-C bond cleavage was reported (Shen et al., 2016). The reaction used an iron-catalyzed

solution of poly(ethylene glycol) in an aqueous solution under oxidant-free conditions to get the desired products (Scheme 20).



Scheme 20. Synthesis of quinolines and quinazolines from 1,3-diketones.

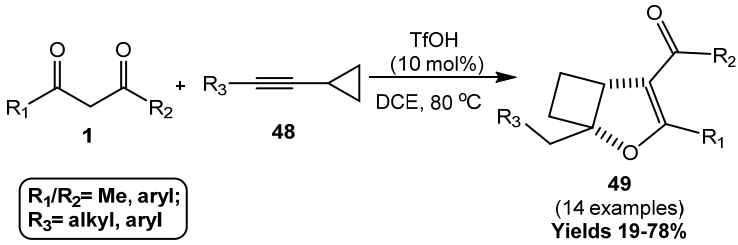
The synthesis of diazepine by reacting 1,3-diketones with *o*-phenylenediamine **46** was reported by Vaddula et al., (2013). The optimized reaction condition for this protocol was subjecting *o*-phenylenediamine **46** (0.5 mmol) and 1,3-diketone (0.55 mmol) to microwave irradiation at 120 °C for 5-20 minutes, getting the diazepines **47** in excellent yields (93–96%) Scheme 21.



Scheme 21. Synthesis of diazepines from 1,3-diketones.

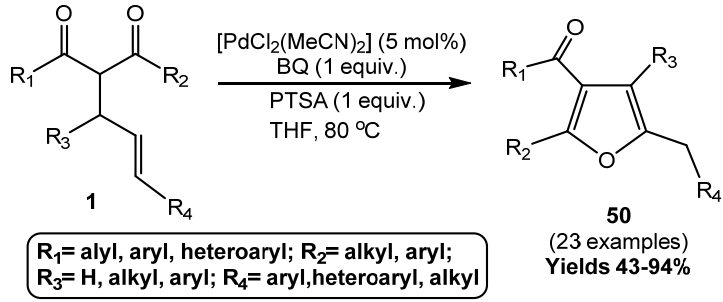
4.2 Synthesis of *O*-containing heterocycles

The trifluoromethanesulfonic acid (TfOH)-catalyzed tandem cyclopropane ring enlargement/C-C formation/etherification reaction between alkynylcyclopropanes **48** and 1,3-diketones giving four-membered carbocycle-fused dihydrofurans **49** that are architecturally interesting was explored by Ye and Yu (2011). A range of aryl and alkyl-substituted 1,3-diketones were compatible in this tandem reaction using dichloroethane (DCE) as the solvent. However, the aryl-substituted 1,3-diketones were better nucleophiles than the alkyl-substituted 1,3-diketones (Scheme 22).



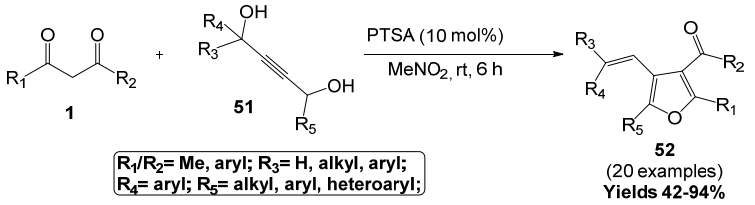
Scheme 22. Synthesis of furan derivatives from 1,3-diketones.

The synthesis of highly functionalized 2-benzyl furans **50** through palladium-catalyzed intramolecular oxidative annulation of 2-cinnamyl-1,3-dicarbonyls **1''** was successfully demonstrated by Nallagonda et al. (2015). The reaction was catalyzed by $[PdCl_2(MeCN)_2]$, in the presence of benzoquinone (BQ) as the oxidant and PTSA as an acid additive in tetrahydrofuran (THF), to give the tetrasubstituted furans in moderate to good yields (Scheme 23).



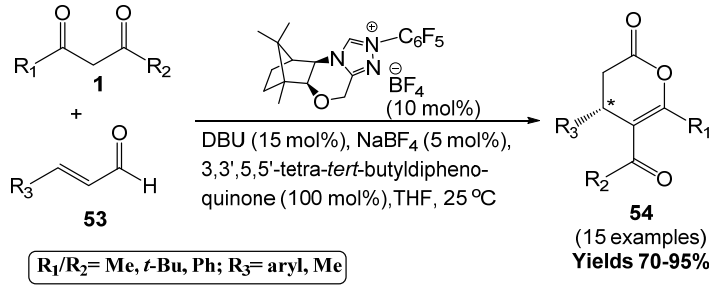
Scheme 23. Synthesis of tetrasubstituted furans from 1,3-diketones.

Mothe et al. (2012) developed a method to prepare tetrasubstituted furans **52** efficiently from cycloisomerization of but-2-yne-1,4-diols **51** with 1,3-diketones catalyzed by PTSA. The orthogonal modes of reactivity of the alcoholic substrates were utilized through slight modification of the reaction conditions resulting in a divergence in product selectivity. The protocol showed that with PTSA as the catalyst and nitromethane ($MeNO_2$) as the solvent, the conditions proved to be broad, resulting in a variety of tetrasubstituted furans that could be furnished in good to excellent yields (Scheme 24).



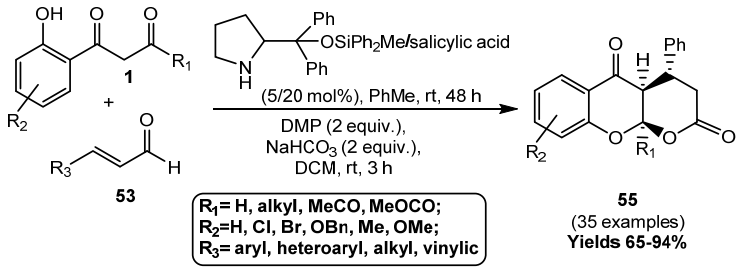
Scheme 24. Synthesis of tetrasubstituted furans from 1,3-diketones.

Rong et al. (2011) developed an enantioselective *N*-heterocyclic carbene (NHC)-catalyzed Michael addition reaction of 1,3-diketones to *α,β*-unsaturated aldehydes **53** using redox oxidation. The reaction was performed in the presence of 10 mol% of camphor-derived triazolium salt, 15 mol% of DBU, 5 mol% of $NaBF_4$ and 100 mol% of 3,3',5,5'-tetra-*tert*-butyldiphenoquinone in THF at 25 °C, giving enantioenriched substituted 3,4-dihydro-α-pyrones **54** in good yields (Scheme 25). However, symmetrical 1,3-diketones with strong electron-withdrawing or bulky groups led to low reactivity and no products were isolated.



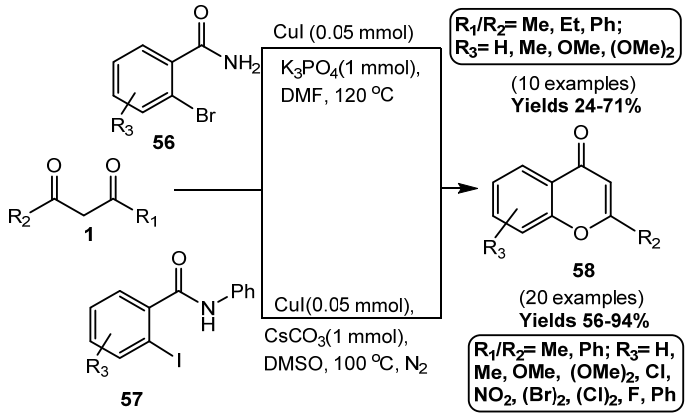
Scheme 25. NHC catalyzed synthesis of 3,4-dihydro-*α*-pyrones using 1,3-diketones.

Lu et al. (2020) developed an enantioselective Michael addition/cycloketalization/hemiacetalization sequence in the presence of a chiral amine catalyst for the facile synthesis of a wide range of lactone-fused tricyclic chromanone derivatives **55** with excellent enantioselectivities and diastereoselectivities from simple 1-(2-hydroxyaryl)-1,3-diketones and *α,β*-unsaturated aldehydes **53** (Scheme 26). It is noteworthy to mention that the R_3 substituents of the *α,β*-unsaturated aldehydes could be in various functional groups, ranging from heteroatom aryl rings to vinyl group and aliphatic substituents. All the cases examined led to good yields of products with 35 examples of up to 94% yield.



Scheme 26. Synthesis of lactone-fused tricyclic chromanones using 1,3-diketones.

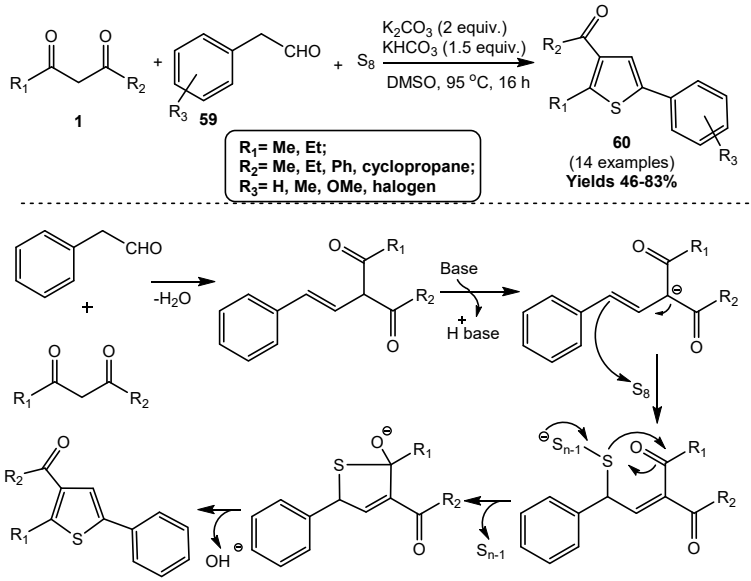
The synthesis of 3-substituted isocoumarins **58** using 1,3-diketones was reported by two groups *viz.* Cai et al. (2012) and Kavala et al., (2012). The former utilized the reaction between *o*-bromobenzamide derivatives **56** and 1,3-diketones *via* CuI-catalyzed in dimethyl formamide (DMF) under the action of K_3PO_4 at 120 °C giving products up to 71% yield. However, the latter used 2-iodo-*N*-phenyl benzamides **57** instead of *o*-bromobenzamides **56** using CuI and $CsCO_3$ in DMSO at 100 °C under N_2. The yields were up to 94% within a short duration (5-60 min) in this method compared to 24 h in the former case (Scheme 27).



Scheme 27. Synthesis of isocoumarins using 1,3-diketones.

4.3 Synthesis of *S*-containing heterocycles

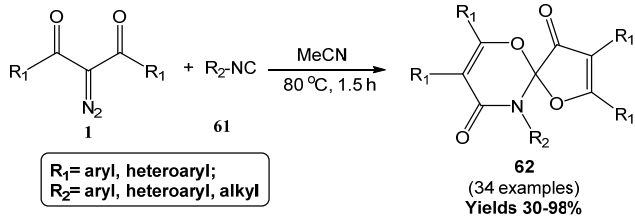
The synthesis of 2-arylthiophenes using the three-component reaction of arylacetaldehydes **59**, 1,3-diketones and elemental sulfur was reported by Huang et al. (2017). This reaction proceeds through the cascade condensation/annulation under the basic buffer system of K_2CO_3 with $KHCO_3$ in DMSO (Scheme 28). It provides a facile entry to 2,3,5-trisubstituted thiophenes **60** with moderate to excellent yields along with good functional group tolerance.



Scheme 28. Synthesis of trisubstituted thiophenes using 1,3-diketones.

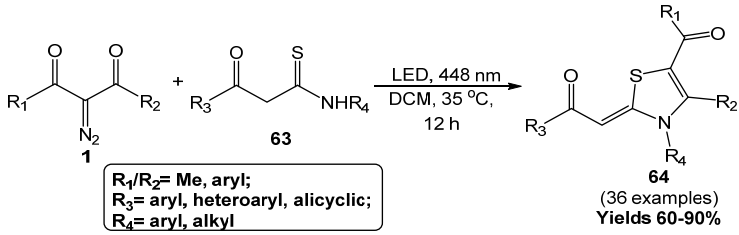
4.4 Synthesis of two-heteroatoms heterocycles

The catalyst-free formal [4+1]/[4+2] cycloaddition of isocyanide **61** with two molecules of acylketene formed *in situ* through the thermal-induced Wolff rearrangement of 2-diazo-1,3-diketones **1** leading to the formation of *O,O,N*-spiro compounds consisting of both 1,3-oxazine and a furan ring **40** was developed (Luo et al., 2020). This protocol displayed good functional group tolerance and was compatible with different isocyanides and 2-diazo-1,3-diketones (Scheme 29).



Scheme 29. Constructing of *O,O,N*-spiro compounds.

Ansari et al. (2020) developed a photocatalyst and visible-light mediated chemoselective domino protocol to access fully substituted thiazoline derivatives **64** from *β*-ketothioamides **63** and *α*-diazo 1,3-diketones at moderate temperature in the open air (Scheme 30). The reaction proceeds through *in situ* generation of electrophilic carbenes from α-diazo 1,3-diketones by a low-energy blue LED (448 nm), which undergoes selective coupling with nucleophilic *β*-ketothioamides to give the desired products by the successive formation of C-S and C-N bonds in one stretch.



Scheme 30. Constructing of fully substituted thiazolines.